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Vascular Risk, Functional Connectivity, and Episodic Memory in Older Adults

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LOYOLA UNIVERSITY CHICAGO

VASCULAR RISK, FUNCTIONAL CONNECTIVITY,
AND EPISODIC MEMORY IN OLDER ADULTS

A DISSERTATION SUBMITTED TO
THE FACULTY OF THE GRADUATE SCHOOL
IN CANDIDACY FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

PROGRAM IN CLINICAL PSYCHOLOGY

BY

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CHICAGO, ILLINOIS

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ABSTRACT

Resting-state functional magnetic resonance imaging and functional connectivity (FC) analyses are used to explore functional brain networks underlying a diverse array of abilities. Functional networks are composed of regions throughout the brain whose activity is closely linked to form a coherent network. One functional network, the “default mode network” (DMN), is thought to subserve self-referential thought and autobiographical memory. DMN regions include the ventromedial prefrontal cortex, inferior parietal lobe, hippocampus, and the primary “hub” of this network, the posterior cingulate cortex (PCC). For reasons yet unknown, DMN FC declines in aging, which is associated with memory impairment. Vascular risk may be an important contributor to age-related DMN disruption through its effects on gray and white matter integrity.

The present study examined relationships among vascular risk, DMN FC, and episodic memory in older adults using FC analyses and structural equation modeling. Several regions found to be functionally related to the PCC were those identified in prior research on the DMN, but also included areas not typically implicated in the DMN, such as the cerebellum and basal ganglia. Stronger FC between the PCC and parahippocampal gyrus predicted better memory performance, confirming the importance of medial temporal lobe structures for memory. FC between the PCC and several other areas, such as the cerebellum, basal ganglia, and limbic regions, also predicted memory performance, suggesting the importance of executive functioning and emotion for memory in aging.

Correlations between FC and vascular risk were found in the basal ganglia, cerebellum, and inferior temporal gyrus, suggesting vascular risk may modify associations between the DMN and cortical and subcortical regions. Finally, a mediational model was tested in which DMN FC mediated the relationship between vascular risk and memory. This was compared to an alternative model with depressive symptoms as a mediator. Vascular risk was unrelated to memory and DMN FC in all models, while stronger DMN FC predicted *poorer* memory performance. Neither DMN FC nor depressive symptoms acted as mediators. The impact of vascular risk on the DMN in aging should be further explored using a comprehensive multimethod approach, along with other potential causes of age-related DMN disruption.

CHAPTER ONE

INTRODUCTION

Advancing age is associated with subtle declines in cognitive functioning, even in the absence of frank neurological disease (Andrews-Hanna, Snyder, Vincent, Lustig, Head, Raichle, & Buckner, 2007; Light, 1991; Lindenberger & Baltes, 1997; Nilsson, 2003; Park, Lautenschlager, Hedden, Davidson, Smith, & Smith, 2002; Park, Smith, Lautenschlager, Earles, Frieske, Zwahr, & Gaines, 1996; Schaie & Willis, 1993; Steiner, Hall, Sliwinski, & Lipton, 2010). Through the advent of neuroimaging methods, which provide non-invasive means of observing the brains of living humans, changes in brain structure and function have also been detected among older adults, revealing insights into the neurobiological underpinnings of cognitive changes observed in old age. One neuroimaging method that has received increasing interest in the literature is resting-state functional magnetic resonance imaging (fMRI; Bandettini, 2009; Cole, Smith, & Beckmann, 2010). Like other fMRI approaches, resting-state fMRI measures the Blood Oxygenation Level Dependent (BOLD) signal, which is an indirect measure of neuronal functioning that relies on the change in magnetic properties of blood flowing to more active regions within the brain (Bandettini, 2009; Buxton, 2010). What is unique about resting-state fMRI is that it images the brain of an individual at rest, without being involved in goal-oriented mental activity. Early trials with resting-state fMRI

revealed that low frequency fluctuations of the BOLD signal, conceptualized as spontaneous neural activity not related to external stimulation, exhibit temporal coherency among spatially distributed brain regions thought to be interconnected in neural networks (Bandettini, 2009; Cole et al., 2010; Sadaghiani, Hesselmann, Friston, & Kleinschmidt, 2010). Following this discovery, resting-state fMRI data have been frequently used in functional connectivity analyses. These analyses compute the temporal correlation of low-frequency BOLD fluctuations among regions throughout the brain as an index of their degree of functional connectedness into neural networks.

One functional network discovered from early resting-state fMRI research has been termed the “default mode network” (DMN) because of its increased activity at rest and attenuated activity during most goal-directed tasks (Buckner, Andrews-Hanna, & Schacter, 2008). The brain regions comprising the DMN include the posterior cingulate cortex (PCC), ventromedial prefrontal cortex, inferior parietal lobule, and hippocampus (Buckner et al., 2008; Laird, Eickhoff, Li, Robin, Glahn, & Fox, 2009). While the exact function of the DMN remains unresolved, the few cognitive tasks which produce increased activation in the DMN have been used to provide clues as to its role in cognition. One proposal is that the DMN underlies self-referential social and emotional thought closely reliant upon autobiographical memory (Bar, 2007; Buckner et al., 2008; D’Argembeau, Collette, van der Linden, Laureys, Del Fiore, et al., 2005; Grigg & Grady, 2010; Gusnard, Akbudak, Shulman, & Raichle, 2001; Hassabis & Maguire, 2007; Raichle, 2006; Wicker, Ruby, Royet, & Fonlupt, 2003). According to this proposal, the DMN is composed of distinct subnetworks interconnected through the action of

subnetwork “hubs” (Buckner et al., 2008). The DMN subnetwork that underlies autobiographical memory is integrated through the PCC hub, while the subnetwork underlying self-referential social and emotional thought convenes on the ventromedial prefrontal cortex hub (Amodio & Frith, 2006; Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010; Buckner & Carroll, 2007; D’Argembeau et al., 2005; Gusnard et al., 2001; Kjaer, Nowak, & Lou, 2002; Piolino, Giffard-Quillon, Desgranges, Chetelat, Baron, & Eustache, 2004; Ries, Schmitz, Kawahara, Torgerson, Trivedi, & Johnson, 2006; Schneider, Bermpohl, Heinzl, Rotte, Walter, et al., 2008; Stawarczyk, Majerus, Maquet, & D’Argembeau, 2011; Uddin, Supekar, & Menon, 2010). This hypothesis corroborates empirical findings suggesting the DMN is preferentially activated by tasks requiring general self-referential thought, autobiographical memory, future-oriented cognition, and inferring another’s thoughts and emotions (Andreasen, O’Leary, Cizaldo, Arndt, Rezai, Watkins, et al., 1995; Buckner et al., 2008; Buckner & Carroll, 2007; D’Argembeau et al., 2005; Gilbert, Spengler, Simons, Steele, Lawrie, Frith, & Burgess, 2006; Gusnard et al., 2001; Macrae, Moran, Heatherton, Banfield, & Kelley, 2004; Mitchell, Heatherton, & Macrae, 2002; Mitchell, Macrae, & Banaji, 2006; Schacter, Addis, & Buckner, 2007; Schilbach, Eickhoff, Rotarska-Jagiela, Fink, & Vogeley, 2008; Spreng, Mar, & Kim, 2009). A second proposal for the role of the DMN is that it acts to direct broad, unfocused attention to monitor the environment (Ghatan, Hsieh, Wirsén-Meurling, Wredling, Eriksson, et al., 1995; Gilbert et al., 2006; Gilbert, Dumontheil, Simons, Frith, & Burgess, 2007; Gusnard & Raichle, 2001; Laird et al., 2009; Shulman, Fiez, Corbetta, Buckner, Miezin, Raichle, & Petersen, 1997). While this proposal agrees

with some past research on the DMN, recent studies attempting to differentiate between the two hypotheses for DMN function have provided stronger support for the former hypothesis emphasizing its role in self-referential thought and autobiographical memory (Andrews-Hanna, Reidler, Huang, & Buckner, 2010; Stawarczyk et al., 2011).

Interestingly, older adults tend to show a reduction in functional connectivity within the DMN when compared to their younger counterparts (Andrews-Hanna et al., 2007; Buckner, Sepulcre, Talukdar, Krienen, Liu, Hedden, et al., 2009; Damoiseaux, Beckmann, Arigita, Barkhof, Scheltens, Stam, Smith, & Rombouts, 2008; Esposito, Aragri, Pesaresi, Cirillo, Tedeschi, Marciano, et al., 2008; Grady, Protzner, Kovacevic, Strother, Afshin-Pour, Wojowicz, et al., 2010; Hedden, Van Dijk, Becker, Mehta, Sperling, Johnson, & Buckner, 2009; Koch, Teipel, Mueller, Buerger, Bokde, Hampel, et al., 2010; Park, Polk, Hebrank, & Jenkins, 2010; Sambataro, Murty, Callicott, Tan, Das, Weinberger, & Mattay, 2010; Wang, LaViolette, O'Keefe, Putcha, Bakkour, Van Dijk, et al., 2010; Wu, Zang, Long, Li, & Chan, 2007; Ystad, Eichele, & Lundervold, 2010). Moreover, older adults also tend to show less DMN de-activation during cognitive tasks than younger adults (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008; Duverne, Motamedinia, & Rugg, 2009; Esposito et al., 2008; Grady, Springer, Hongwanishkul, McIntosh, & Winocur, 2006; Grady et al., 2010; Koch et al., 2010; Lustig, Snyder, Bhakta, O'Brien, McAvoy, Raichle, et al., 2003; Miller, Celone, Depeau, Diamond, Dickerson, Rentz, et al., 2008; Park et al., 2010; Persson, Lustig, Nelson, & Reuter-Lorenz, 2007; Sambataro et al., 2010). In other words, whereas younger adults show less functional activation within DMN regions during most cognitive tasks, older adults show

a failure of the DMN regions to de-activate during such cognitive processing. Some have proposed this age-related failure of DMN deactivation is evidence of compensatory efforts in the aging brain, wherein older adults recruit additional brain regions than younger adults to maintain task performance in response to subtle neuropathological changes (Andrews-Hanna et al., 2007; Goh & Park, 2009; Park & Reuter-Lorenz, 2009; Raz, Lindenberger, Rodrigue, Kennedy, Head, Williamson, et al., 2005). This proposal is closely related to the theory of age-related dedifferentiation of brain regions, such that older adults show less specific responding of brain regions than younger adults do (Goh, 2011). This less specific responding of older adult brains has also been conceptualized as a compensatory response allowing older adults to maintain the same level of task performance by recruiting a wider expanse of neural resources (Cabeza, Anderson, Locantore, & McIntosh, 2002). A second theory to explain the failure of DMN deactivation among older adults is that it results from an inability to effectively shift neural resources from “default mode” processing to task-related processing in other brain networks (Clapp, Rubens, Sabharwal, & Gazzaley, 2011; Grady et al., 2006; Grady et al., 2010; Lustig et al., 2003; Park et al., 2010; Persson et al., 2007). This theory has garnered some support in the literature and suggests that aging is accompanied by an attenuated ability to flexibly shift neural resources according to processing demands in the environment.

It may be that alterations in DMN connectivity explain at least some of the cognitive deterioration noted among relatively healthy older adults. Indeed, reduction in DMN connectivity and failure of DMN de-activation with advancing age have been

associated with cognitive deficits in several domains, including episodic memory (Greicius, Srivastava, Reiss, & Menon, 2004; He, Carmichael, Fletcher, Singh, Iosif, Martinez, et al., 2012; Wang, Liang, Wang, Tian, Zhang, et al., 2007; Wang, Zang, He, Liang, Zhang, Tian, et al., 2006; Wang et al., 2010; Wu et al., 2007). Yet, why the DMN exhibits connectivity reduction in old age and how this impacts cognitive functioning remains unclear. Both functional connectivity and cognitive performance are dependent upon intact gray and white matter within the brain. Consequently, disruptions in gray and white matter integrity, which commonly occur in typically aging older adults, have been associated with reduced DMN connectivity as well as impairments in several cognitive domains (Andrews-Hanna et al., 2007; Chen, Chou, Song, & Madden, 2009; Duong, Audoin, Boulanouar, Ibarrola, Malikova, Confort-Gouny, et al., 2005; Gong, Rosa-Neto, Carbonell, Chen, He, & Evans, 2009; Salthouse, 2011; Seeley, Crawford, Zhou, Miller, & Greicius, 2009).

Ultimately, however, it will be vital to identify the mechanism underlying changes in gray and white matter and subsequent DMN functional connectivity alterations among older adults. This will allow for the creation of early interventions to prevent neural abnormalities and concomitant cognitive decline in the ever-growing older adult population. One extremely common health factor also associated with gray and white matter changes is vascular risk. Indeed, vascular risks, such as hypertension, diabetes, and smoking, are becoming increasingly prevalent in old age and are known to produce disruptions in white matter integrity as well as gray matter atrophy (Appel, Potter, Bhatia, Shen, Zhou, Greig, et al., 2009; Appelman, Exalto, van der Graaf,

Biessels, Mali, & Geerlings, 2009; Bresser, Tiehuis, van den Berg, Reijmer, Jongen, Kappelle, et al., 2010; Brickman, Reitz, Luchsinger, Manly, Shupf, Muraskin, et al., 2010; Bruehl, Wolf, Sweat, Tirsi, Richardson, & Convit, 2009; Burgmans, van Bortel, Gronenschild, Vuurman, Hofman, Uylings, et al., 2010; CDC, 2011; Domino, 2008; Gons, de Laat, van Norden, van Oudheusden, van Uden, Norris, et al., 2010; Gottesman, Coresh, Catellier, Sharrett, Rose, Coker, et al., 2010; He, Iosif, Lee, Martinez, Ding, Carmichael, et al., 2010; Kuller, Margolis, Gaussoin, Bryan, Kerwin, Limacher, et al., 2010; Lazarus, Prettyman, & Cherryman, 2005; Lee, Fletcher, Martinez, Zozulya, Kim, Tran, et al., 2010; Longstreth, Arnold, Manolio, Burke, Bryan, Jungreis, et al., 2000; Ong, Cheung, Man, Lau, & Lam, 2007; Raz, Rodrigue, Kennedy, & Acker, 2007; van Harten, de Leeuw, Weinstein, Scheltens, & Biessels, 2006). Moreover, vascular risk factors are also associated with cognitive declines in otherwise healthy older adults, including declines in episodic memory (Bangen, Delano-Wood, Wierenga, McCauley, Jeste, Salmon, & Bondi, 2010; Brady, Spiro, & Gaziano, 2005; Edelstein, Kritz-Silverstein, & Barrett-Connor, 1998; Elias, Sullivan, D'Agostino, Elias, Beiser, Au, et al., 2004; Harrington, Saxby, McKeith, Wesnes, & Ford, 2000; Hill, Nilsson, Nyberg, & Backman, 2003; Kalmijn, van Bortel, Verschuren, Jolles, & Launer, 2002; Luchsinger, Reitz, Honig, Tang, Shea, & Mayeux, 2005; Paul, Brickman, Cohen, Williams, Niaura, Pogun, et al., 2006; Richards, Jarvis, Thompson, & Wadsworth, 2003; Sabia, Marmot, Dufouil, & Singh-Manoux, 2008; Schinka, Belanger, Mortimer, & Graves, 2003; Singh-Manoux & Marmot, 2005; Starr, Deary, Fox, & Whalley, 2006; Stewart, Deary, Fowkes, & Prince, 2006; Zade, Beiser, McGlinchey, Au, Seshadri, Palumbo, Wolf, et al., 2010).

Despite the relevance of vascular risk for neurological outcomes among older adults, very few studies have considered the impact of vascular risk on functional connectivity. What few studies have addressed this question have suggested that vascular risk is indeed associated with decreased functional connectivity within the brain (Duinkerken, Klein, Schoonenboom, Hoogma, Moll, Snoek, et al., 2009; Sun, Qin, Zhou, Xu, Qian, Tao, & Xu, 2011; Zhou, Lu, Shi, Bai, Chang, Yuan, Teng, & Zhang, 2010).

However, no study in the literature has concurrently examined the impact of vascular risk on both DMN functional connectivity and episodic memory in a sample of older adults. Such a design would provide insight into the role of vascular risk factors in producing functional connectivity alterations and concomitant declines in episodic memory in older adults and would suggest avenues for early intervention to prevent age-related cognitive decline. The present study sought to contribute to the literature by addressing this important issue. Data from a sample of 152 community-dwelling older adults recruited for a larger longitudinal study was obtained and included data from resting-state fMRI, medical interview, and neuropsychological testing. The association of vascular risk with functional connectivity of the PCC, the primary DMN hub, and episodic memory was assessed, as well as the ability of PCC functional connectivity to partially mediate the relationship between vascular risk and episodic memory in this sample. As an additional test of the proposed mediational model, a second alternative model was also tested in which depressive symptomatology acted as the mediator between vascular risk and episodic memory in lieu of PCC functional connectivity. This alternative model is based on research suggesting that vascular risk factors are closely

linked with depression among older adults (Hakim, 2011; Lezak, Howieson, & Loring, 2004; Sneed & Culang-Reinlieb, 2011), and that depression has also been found to impair episodic memory in this population (Bennett, Wilson, Schneider, Bienias, & Arnold, 2004; Hakim, 2011; Lezak et al., 2004; Sneed & Culang-Reinlieb, 2011).

In the following sections, an introduction to basic neuroanatomy will first be provided, followed by an overview of concepts related to resting state fMRI and functional connectivity analyses. Second, findings from functional connectivity analyses among older adults will be discussed, with special emphasis on the DMN and its primary hub, the PCC. Third, associations of altered PCC functional connectivity with episodic memory will be reviewed. Fourth, neurobiological mechanisms driving functional connectivity changes in old age will be explored, culminating with a discussion of vascular risk as a potential cause for altered DMN functional connectivity among older adults. Following the review of literature, the current study will be described along with hypotheses, findings, and implications.

CHAPTER TWO

REVIEW OF RELATED LITERATURE

Resting-State Functional Magnetic Resonance Imaging

The brain is composed of billions of brain cells, called neurons. The brain is divided into gray and white matter according to the predominant neuronal structures found in that brain region. Gray matter, mostly found in the outer layer of the brain called cortex as well as in structures deep within the brain, is composed of neuronal cell bodies which provide its gray color. In contrast, white matter, found in the inner tissue of the brain below the cortex, is composed of axonal projections of neurons. Many axons are coated with myelin, which produces the color of white matter. In order for phenomena such as cognition to occur, neurons must communicate with one another through electrochemical signaling. These signals are propagated down the axonal projection of a neuron, which interfaces with the receptive projections, called dendrites, of the neuron receiving the signal. Figure 1 below depicts the typical structure of a neuron. While science has studied brain structure for many years, methods to accurately measure and understand brain function have been elusive until relatively recently.

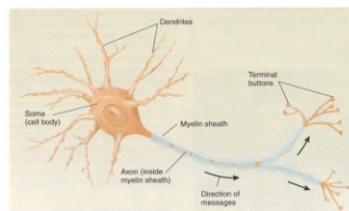


Figure 1. Structure of a typical neuron (Carlson, 2007)

The advent of functional neuroimaging, including functional magnetic resonance imaging (fMRI), has allowed researchers and clinicians to non-invasively observe neural processing in health and disease (Bandettini, 2009; Bassett & Bullmore, 2009; Guidotti Breting, Tuminello, & Han, 2012). Increased accessibility to functional imaging methods has produced a subsequent explosion in research examining brain function throughout the lifespan, significantly expanding the field's understanding of neural activity and the brain networks thought to underlie it. fMRI is a commonly used method for observing brain activity, and measures the Blood Oxygenation Level Dependent (BOLD) signal (Buxton, 2010). The BOLD signal is a measure of blood oxygenation in the brain. When a brain region becomes active, blood flow to that region increases presumably due to neuronal activity. While this happens, the amount of oxygen in the blood flowing to the active region also increases because the amount of oxygen extracted by the active brain region is exceeded by the amount being supplied through the increased blood flow. This increase in blood oxygenation alters the magnetic properties of the blood flowing to the region, resulting in a magnetic difference that can be detected by MRI magnets in the form of the BOLD signal. Thus, increases in the BOLD signal detected by fMRI machines are interpreted as increases in brain activity within the given brain region. Importantly, then, the BOLD signal is not a direct measure of neuronal activation, but is instead used as a proxy to infer the presence of neural activation (Bandettini, 2009; Buxton, 2010).

A recent movement in the field of cognitive neuroscience has gone beyond considering isolated brain regions to explore complex neural networks composed of many brain regions working together to support varied cognitive processes, such as

memory. Although not exclusively, these investigations often image brain activity while a person is at rest, termed in some places in the literature as resting-state fMRI (Bandettini, 2009; Cole et al., 2010). This form of fMRI is distinct from common task-related functional neuroimaging paradigms in that a person is simply asked to lie in the imaging scanner with their eyes closed, although specific instructions given vary by study (Benjamin, Lieberman, Chang, Ofen, Whitfield-Gabrieli, Gabrieli, & Gaab, 2010; Van Dijk, Hedden, Venkataraman, Evans, Lazar, & Buckner, 2010). The benefit of resting-state fMRI is that the absence of a task produces relatively short scanning times and a lower margin of acquisition error, allowing for cost-efficient and rapid acquisition of large amounts of functional imaging data (Cole et al., 2010; Guidotti Breting et al., 2012). When researchers are interested in functionally associated networks of brain regions, data collected with resting-state fMRI are utilized in functional connectivity (FC) analyses. FC analyses take advantage of the fact that the BOLD signal detected in fMRI is not constant, but fluctuates in concert with neural activity as well as other factors (e.g., heart rate, respiration). These BOLD signal fluctuations occur at many different frequencies, measured in Hertz (Hz). Importantly, the source of BOLD signal fluctuations can be identified in some respects through the frequency of the given BOLD signal. FC analyses examine low-frequency (i.e., at or below 0.1 Hz) fluctuations in the BOLD signal, also called “endogenous oscillations,” because fluctuations at this frequency have been associated with spontaneous neural activity when the brain is not engaged in a task (Bandettini, 2009; Cole et al., 2010; Sadaghiani et al., 2010). The result of FC analyses is often a set of correlations representing the degree to which the BOLD signal fluctuations

in different brain regions are temporally linked with one another. Brain regions with a high degree of correlation in their BOLD signals are interpreted as belonging to a functionally-associated network of brain regions. The most well-known network identified using resting-state FC analyses has been termed the “default mode network” (DMN; Buckner et al., 2008). The DMN is thought to consist of a network of functionally connected brain regions including posterior cingulate cortex (PCC), ventromedial prefrontal cortex, dorsal medial prefrontal cortex, inferior parietal lobule, hippocampus, and lateral temporal cortex (Buckner et al., 2008; Laird et al., 2009), and is thought to be involved in internally-oriented, self-relevant thought and autobiographical memory (Bar, 2007; Buckner et al., 2008; D’Argembeau et al., 2005; Grigg & Grady, 2010; Gusnard et al., 2001; Hassabis & Maguire, 2007; Raichle, 2006; Wicker et al., 2003). As will be discussed, much research has examined the DMN to determine its purpose and potential involvement in neurodegenerative diseases.

As in any other field of research which examines phenomena not readily observed without the support of advanced techniques, much work has attempted to validate the functional neural networks identified in FC analyses. Supporting their validity, composition of the identified networks has been replicated across studies, including those with different functional imaging modalities (e.g., PET) and tasks, different individuals, different points in time within individuals, stages of development, states of consciousness, and even in different species (Bandettini, 2009; Buckner et al., 2009; Cole et al., 2010; Damoiseaux, Rombouts, Barkhof, Scheltens, Stam, Smith, & Beckmann, 2006; Margulies, Vincent, Kelly, Lohmann, Uddin, Biswal, Villringer, et al., 2009;

Pawela, Biswal, Cho, Kao, Li, Jones, et al., 2008; Shehzad, Kelly, Reiss, Gee, Gotimer, Uddin, et al., 2009; Vincent, Patel, Fox, Snyder, Baker, Van Essen, et al., 2007; Zuo, Di Martino, Kelly, Shehzad, Gee, et al., 2010; Zuo, Kelly, Adelstein, Klein, Castellanos et al., 2010). For instance, one study pooled resting-state fMRI data from 35 laboratories and replicated functional networks across each of these datasets (Biswal, Mennes, Zuo, Gohel, Kelly, Smith, et al., 2010). Resting-state fMRI identified networks are also consistent with networks identified using task-dependent functional neuroimaging paradigms (Smith, Fox, Miller, Glahn, Fox, Mackay, et al., 2009). Furthermore, and perhaps most persuasively, findings from diffusion tensor imaging (DTI) and other neuroimaging methods which identify structural white matter connections among brain regions (i.e., tracts within the brain composed of neuronal axon projections), have commonly mirrored networks identified using resting-state functional connectivity (Bassett & Bullmore, 2009; Greicius, Supekar, Menon, & Dougherty, 2009; Honey, Sporns, Cammoun, Gigandet, Thiran, Meuli, & Hagmann, 2009; Teipel, Bokde, Meindl, Amaro, Soldner, Reiser, et al., 2010; van den Heuvel, Mandl, Kahn, & Pol, 2009). This suggests that the correlations in activity across spatially distributed brain regions are explained, at least in part, by physical white matter connections among these regions, which is what one would expect should FC analyses indeed identify valid neural networks. The close association of functional networks with white matter connections composing structural brain networks is not surprising, given that white matter tracts are composed of myelinated axonal projections from one neuron to another, and groups of neurons to other groups of neurons. These axonal projections allow neurons to

communicate directly through electrochemical signaling, which ostensibly contributes to the temporal correlations among their BOLD signals as identified in FC analyses.

However, research has also found that functional neural networks are not entirely explained by direct structural connections among brain regions (Biswal et al., 2010; Honey et al., 2009; Greicius et al., 2009). For instance, Honey and colleagues (2009) collected resting state fMRI and DTI data from five healthy adult participants and used DTI measures of structural connectivity to model functional connectivity with computational modeling. Results revealed that while functional connectivity was explained by direct structural connectivity in some cases, it was also common for regions to be functionally connected without direct structural connections between them. In these cases, indirect connections among regions (e.g., regions indirectly connected through an intermediate brain region) explained additional variance in functional connectivity levels (Honey et al., 2009). Thus, although functional connectivity may not always imply direct structural connectivity among regions, it does conform to the overarching structure of anatomical connections present throughout the cortex when indirect structural connections are taken into account (Biswal et al., 2010; Buckner et al., 2008; Honey et al., 2009).

A complementary hypothesis regarding the imperfect correlation between structural and functional connectivity is that, while functional connectivity is broadly organized according to structural connectivity, it is further modulated by context-dependent factors (Albert, Robertson, & Miall, 2009; Biswal et al., 2010; Buckner et al., 2009; Harrison, Pujol, Lopez-Sola, Hernandez-Ribas, Deus, Ortiz, et al., 2008; Moussa,

Vechlekar, Burdette, Steen, Hugenschmidt, & Laurienti, 2011; Sadaghiani et al., 2010).

In support, variations in FC occur following the learning of new material and changes in FC predict subsequent changes in behavior (Albert et al., 2009; Bandettini, 2009; Lewis, Baldassarre, Committeri, Romani, & Corbetta, 2009; Sadaghiani et al., 2010). Moreover, the impact of activity in functional networks on behavioral performance changes according to the task at hand (Sadaghiani et al., 2010). For instance, activity in the default mode network (DMN) is typically inversely related with task performance accuracy.

However, during an auditory perception task, low-frequency fluctuations in the posterior cingulate cortex (PCC), an important region in the DMN, was associated with *higher* perception accuracy (Sadaghiani et al., 2010). The authors suggested this counterintuitive finding occurred due to participants retrieving the memory of the auditory stimulus before responding that they had perceived it on a given trial, and that this remembering was mediated by PCC activity, as the region is implicated in episodic memory. In a study using graph theory, Moussa and colleagues (2011) examined whole-brain and regional network properties during rest, visual, and multisensory tasks. They found that while the mean whole-brain network characteristics remained the same across tasks, the regional network characteristics, including clustering, path length, and modularity, varied according to task, with brain regions relevant to task characteristics becoming more important network hubs in those tasks. Both of these studies suggest that functional networks exhibit both stable and dynamic context-dependent properties. While the nature of functional networks may not be as simple as the perfect structure-function correlation originally anticipated, investigating the nature of FC changes according to different tasks

can shed light on the function of specific neural networks and the overall functional organization of the brain (Moussa et al., 2011).

Despite the burgeoning amount of research utilizing resting-state fMRI and functional connectivity analyses, many controversies exist regarding the interpretation of resting-state fMRI activity, spontaneous low frequency BOLD signal fluctuations, and FC analyses (Morcom & Fletcher, 2007). First, although the term “resting-state” infers the absence of goal-directed activity in the brain, the lack of a structured task during scanning does not preclude the occurrence of spontaneous cognitive processes. Thus, critics purport that brain activity found during resting-state fMRI may be impacted by what exactly participants are thinking about while in the scanner. However, empirical support for instruction-related differences in neural activity identified using resting-state fMRI has been inconsistent (Benjamin et al., 2010; Cole et al., 2010). Some have reported activity differences depending on whether instructions are given to keep eyes open or closed, on whether to allow one’s mind to wander or attempt to keep their mind blank, and so on (Benjamin et al., 2010; Yan, Liu, He, Zou, Zhu, et al., 2009). However, others have reported that such differences in rest instructions do not have a significant impact on resting state activity, or perhaps more importantly, functional connectivity results (Cole et al., 2010). In fact, the potential variability in cognitive activity among participants produced by the unstructured nature of resting tasks can be used as data to further understand the function of resting-state networks, particularly the DMN (Buckner et al., 2008). Simply asking participants what they were thinking about while being

scanned can provide insights into the function of resting-state networks (Buckner et al., 2008).

A second controversy is the interpretation of spontaneous low frequency BOLD signal fluctuation. The low frequency band on which FC analyses focus may be composed of signals from a range of sources beyond neuronal activity, including respiratory and cardiovascular activity, as well as scanning artifacts (Bandettini, 2009; Cole et al., 2010). However, research has shown that low frequency BOLD signal fluctuations are temporally and spatially linked to electroencephalographic indices of neuronal activity and can be differentiated from frequencies produced by physiological factors (Bandettini, 2009; Cole et al., 2010; Cordes, Haughton, Arfanakis, Carew, Turski, et al., 2000; Sadaghiani et al., 2010). Nevertheless, physiological and scanning artifacts may still impact spontaneous brain activity detected in the resting state (Bandettini, 2009; Cole et al., 2010). This is particularly important when using fMRI with older adults, because the neurovascular coupling on which the BOLD signal depends may be reduced with advancing age (Bangen, Restom, Liu, Jak, Wierenga, Salmon, & Bondi, 2009; Buckner, Snyder, Sanders, Raichle, & Morris, 2000; D'Esposito, Deouell, & Gazzaley, 2003; Kannurpatti, Motes, Rypma, & Biswal, 2010; Riecker, Grodd, Klose, Schulz, Groschel, Erb, Ackermann, & Kastrup, 2003). Yet, a recent study with younger and older adults found that vascular variability in old age only affected performance on motor tasks and that age differences in cognitive tasks were instead related to alterations in neural activity (Kannurpatti et al., 2010). Moreover, data processing procedures are available to

account for these potential confounding factors and maximize the signal-to-noise ratio present in the fMRI data (Bandettini, 2009; Cole et al., 2010).

An important conceptual question which remains unresolved is an understanding of the *function* of low frequency BOLD signal fluctuations (Bandettini, 2009; Pizoli, Shah, Snyder, Shimony, Limbrick, Raichle, et al., 2011; Sadaghiani et al., 2010).

Assuming that the fluctuations represent spontaneous neuronal activity as opposed to physiological or scanning artifacts, what do these low frequency fluctuations represent and what function do they serve (Bandettini, 2009)? As previously mentioned, research in this area has already suggested the functional relevance of low frequency fluctuations, for instance, finding that they explain a significant amount of variance in motor performance or external stimulus perception (Bandettini, 2009; Sadaghiani et al., 2010). Some have theorized that low frequency fluctuations allow the brain to flexibly deal with future events (Buckner et al., 2008; Miall & Robertson, 2006; Pizoli et al., 2011; Raichle, 2010; Uddin et al., 2010), while others propose that they support the development and maintenance of neural networks through promoting synaptogenesis (Doria, Beckmann, Arichi, Merchant, Groppo, Turkheimer, et al., 2010; Pizoli et al., 2011; Seeley et al., 2009; Supekar, Uddin, Prater, Amin, Greicius, & Menon, 2010; Zielinski, Gennatas, Zhou, & Seeley, 2010). Indeed, a separate body of literature supports the role of spontaneous neuronal activity in promoting synaptic development and plasticity (Katz & Shatz, 1996; Liu, Yu, Liang, Li, Tian, Zhou, et al., 2007; Pizoli et al., 2011; Sha & Crair, 2008). These findings shed light on some of the potential functions of low frequency

fluctuations in neural activity, but the full range of their functional significance likely remains underappreciated.

Controversies also exist in interpreting results from functional connectivity analyses. Functional relationships among individual brain regions within and across functional networks may change over time, producing variability in resting-state networks (Bassett & Bullmore, 2009; Calhoun, Kiehl, & Pearlson, 2008; Chang & Glover, 2010; Grigg & Grady, 2010; Moussa et al., 2011; Sadaghiani et al., 2010; Stevens, Buckner, & Schacter, 2010; Waites, Stanislavsky, Abbott, & Jackson, 2005). For instance, Honey et al. (2009) examined temporal reliability of functional connectivity among five healthy adult participants within and across two scanning sessions. While FC values between any two given regions were significantly correlated across time, the correlations were lower than may be expected (e.g., correlations ranged from $r = 0.38$ to 0.69 across scanning sessions). It is nevertheless important to note that among resting-state networks that are strongly functionally related or have strong structural connections, such as the default mode network, temporal reliability was increased (Honey et al., 2009). Moreover, as previously discussed, some have suggested that such variability in resting-state FC is an inherent quality of functional networks that allows the functional connectivity among its components to be modulated by context-dependent factors (Bassett & Bullmore, 2009; Sadaghiani et al., 2010). In fact, a recent study by Grigg and Grady examined spatial and temporal reliability of DMN connectivity. They found two patterns of DMN FC often occurring simultaneously, one robust pattern of FC that was stable across time and contexts, and another secondary pattern that was more variable and

dependent on cognitive tasks being performed prior to the resting state (Grigg & Grady, 2010). Thus, multiple lines of evidence converge to suggest that, while functional networks have a relatively stable pattern of connectivity among regions, this pattern can be temporarily modulated by cognitive activity. As others have noted, this characteristic of resting state networks can provide interesting fodder for future research, but at the same time must be taken into careful consideration when analyzing FC in resting states following a cognitive task.

A final factor that increases variability in functional connectivity analyses are the analytic strategies chosen to identify resting state networks. Two analytic strategies are most commonly employed, namely seed-based correlation analyses and independent components analysis (ICA), although other strategies, such as graph theory, are available (Cole et al., 2010; Koch et al., 2010). Each strategy has its own strengths and weaknesses, and while the networks identified by each strategy often overlap, differences between them, even when performed in the same participants, can be found. For instance, in seed-based correlation analyses, the researcher selects a seed-region, usually a specific voxel or larger region of interest (ROI) in the brain, and identifies every voxel in the brain whose activity is significantly correlated with this seed region. Thus, resultant correlation maps differ depending on the seed region chosen (Sadaghiani et al., 2010). Similarly, FC results using ICA can differ depending on the number of components extracted, and then interpretation of extracted components can be very difficult. User-dependent settings chosen within a specific analytic strategy can further impact resultant functional networks (Sadaghiani et al., 2010). For example, while some researchers seek

to identify large, coherent networks within the brain, others seek to make fine-grained distinctions between and within larger functional networks. These different perspectives on how one should investigate the functional organization of the brain can lead to identification of different numbers functional networks, particularly in data-driven (e.g., ICA) approaches (Sadaghiani et al., 2010). Therefore, although the functional networks identified with these various analytic strategies are largely convergent, it should be noted that analytically-mediated differences often emerge (Sadaghiani et al., 2010).

The Default Mode Network

Perhaps the most frequently investigated functional network has been the default mode network (DMN; Buckner et al., 2008; Gusnard & Raichle, 2001; Gusnard et al., 2001; Raichle MacLeod, Snyder, Powers, Gusnard, et al., 2001). The DMN is a network of brain regions including the ventromedial prefrontal cortex, posterior cingulate cortex, inferior parietal lobule, lateral temporal cortex, dorsomedial prefrontal cortex, and the hippocampal formation (Buckner et al., 2008; Laird et al., 2009). Figure 2 below depicts regions typically thought to be involved in the DMN.

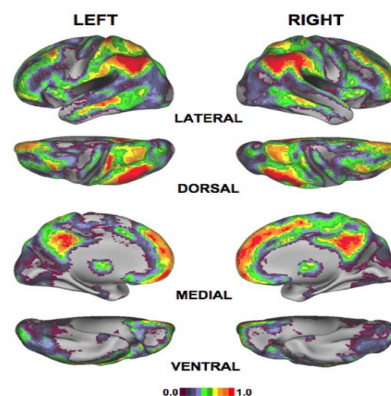


Figure 2. fMRI image of the DMN network (in warm tones; Buckner et al., 2009).

The term “default mode” arose from consistent observations that the DMN is more active during passive, resting states and less active during goal-directed tasks (Buckner et al., 2008; Gusnard & Raichle, 2001; Gusnard et al., 2001; Mazoyer, Wicker, & Fonlupt, 2002; Mazoyer, Zago, Mellet, Bricogne, Etard, Houde, et al., 2001; Raichle et al., 2001; Shulman et al., 1997). The DMN is often found to be anticorrelated (i.e., activity levels are inversely related) with the “task positive network,” a network of brain regions that is more active during task performance than when at rest (Fox, Snyder, Vincent, Corbetta, Van Essen, & Raichle, 2005). The DMN was first discovered incidentally when researchers noted a common set of brain regions was more active in “control” resting states compared to task performance (Buckner et al., 2008). Subsequent meta-analyses of studies using positron emission tomography (PET; Mazoyer et al., 2001; Shulman et al., 1997) and fMRI (Laird et al., 2009) confirmed that, across studies comparing rest conditions to different types of tasks, the same network of brain regions became more active at rest (Buckner et al., 2008). Importantly, results from many different imaging modalities (e.g., fMRI, PET) and analysis strategies (e.g., functional connectivity, task-induced deactivations) have converged on this common set of brain regions as components of the DMN, and have confirmed their coherence in altered states of consciousness, including deep sleep and sedation (Boly, Phillips, Tshibanda, Vanhaudenhuyse, Schabus, Dang-Vu, et al., 2008; Buckner et al., 2008; Horowitz, Fukunaga, de Zwart, van Gelderen, Fulton, Balkin, & Duyn, 2008). Moreover, homologues of DMN brain regions in humans are also found in monkeys and conform to a similar functional and structural connectivity pattern (Buckner et al., 2008).

Although the existence of the DMN has been well-established, full understanding of its function remains elusive. Diverse methods have been employed to investigate DMN function, including examination of tasks that deactivate the DMN, examination of a small number of tasks that preferentially activate the DMN, and examination of cognitive states and patient populations in which DMN connectivity is disrupted. From these investigations, many functions of the DMN have been proposed and can be divided into two categories, involvement in internally focused, self-relevant thoughts and spontaneous cognition, and broad attentional monitoring of the external environment (Andrews-Hanna et al., 2009; Buckner & Carroll, 2007; Buckner et al., 2008; Buckner & Vincent, 2007; Gusnard & Raichle, 2001; Laird et al., 2009). Proposed DMN functions related to spontaneous cognition include episodic memory (Buckner, Snyder, Shannon, LaRossa, Sachs, Fotenos, et al., 2005; Buckner et al., 2008; Greicius, Krasnow, Reiss, & Menon, 2003; Greicius et al., 2004; Greicius & Menon 2004; Kim, Daselaar, & Cabeza, 2010; Kim, 2010; Spreng et al., 2009; Spreng & Grady, 2010), imagining the future (Buckner et al., 2008; Schacter et al., 2007; Spreng et al., 2009; Spreng & Grady, 2010), taking the perspectives of others (Buckner et al., 2008; Schilbach et al., 2008; Spreng et al., 2009; Spreng & Grady, 2010), and more generally, cognition that is relevant to the self (Buckner & Carroll, 2007; D'Argembeau et al., 2005; Goldberg, Harel, & Malach, 2006; Grigg & Grady, 2010; Gusnard et al., 2001; Northoff, Heinzel, de Greck, Bermpohl, Dobrowolny, et al., 2006; Schmitz & Johnson, 2007; Schneider et al., 2008; Stawarczyk et al., 2011; Wicker et al., 2003). Such a variety of proposed DMN functions speaks to the increasing appreciation of the DMN as a large network composed of

multiple closely interacting subsystems (Buckner et al., 2008; Hassabis, Kumaran, & Maguire, 2007; Stawarczyk et al., 2011).

Much research has provided support for the hypothesis that the DMN is generally involved in spontaneous, stimulus independent thoughts (SITs, Andrews-Hanna et al., 2010; Buckner et al., 2008; Christoff, Gordon, Smallwood, Smith, & Schooler, 2009; Gusnard & Raichle, 2001; Mason, Norton, Van Horn, Wegner, Grafton, & Macrae, 2007; McGuire, Paulesu, Frackowiak, & Frith, 1996; McKiernan, D'Angelo, Kaufman, & Binder, 2006). Several studies have examined participants' number of reported SITs at rest and during task performance and have found that the number of reported SITs correlated with the degree of DMN activity (McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003; McKiernan et al., 2006). Furthermore, DMN activity is correlated with individual differences in the tendency to have SITs, with participants who report a greater tendency toward daydreaming showing increased DMN activity compared to others with a lower tendency to daydream (Mason et al., 2007). In a related line of research, others have demonstrated that lapses in attention during task performance, when presumably the participant shifts from external attention to internally focused cognition, is associated with DMN activity, particularly in the PCC (Weissman, Roberts, Visscher, & Woldorff, 2006). Consequently, activity in the DMN during task performance is typically associated with reduced performance on the task, further suggesting that increased DMN activity implies neural resources are being devoted to internal thought instead of externally focused task performance (Eichle, Debener, Calhoun, Specht, Engel, Hugdahl, et al., 2008; Polli, Barton, Cain, Thakkar, Rauch, & Manoach, 2005; Weissman et al., 2006).

For instance, one study of incidental learning of words found that the timing of increased activity in DMN hubs, including the PCC and inferior parietal lobule, predicted which words would later be forgotten by participants (Otten & Rugg, 2001).

An examination of the content of individuals' stimulus-independent thoughts has revealed a tendency toward those that are personally or socially relevant, many of them future oriented (Andreasen et al., 1995; Andrews-Hanna, Huang, Reidler, & Buckner, 2008; Mitchell, 2006; Shilbach et al., 2008). Consequently, the DMN has also been proposed to be particularly important for self-referential thought, including episodic, autobiographical memory, imagining the future, and theory of mind, or taking the perspective of another (Buckner et al., 2008; Buckner & Carroll, 2007; Grigg & Grady, 2010; Oschner, Knierim, Ludlow, Hanelin, Ramachandran, Glover, & Mackey, 2004; Schacter & Addis, 2009; Spreng et al., 2009; Stawarczyk et al., 2011). In fact, a recent meta-analysis delineated the neural networks underlying autobiographical memory, navigation, theory of mind, and rest-related activity across several studies and then performed a conjunction analysis to determine the areas of overlap across these networks, revealing the involvement of the DMN in each examined task (Spreng et al., 2009).

The putative role of the DMN in episodic autobiographical memory is not surprising considering the close association of the DMN with the PCC as well as medial temporal lobe structures, all of which are involved in episodic memory (Andrews-Hanna et al., 2009; Buckner et al., 2008; Lou, Luber, Crupain, Kennan, Nowak, Kjaer, et al., 2004; Lundstrom, Ingvar, & Petersson, 2005; Spreng et al., 2009). Indeed, recalling autobiographical memories has been associated with increased activity in the DMN

(Andreasen et al., 1995; Buckner & Carroll, 2007; Schacter et al., 2007). One study examined correlations of hippocampal FC with participants' report of amount of spontaneous thoughts about the past and future, finding that more spontaneous past or future-oriented thoughts were associated with increased FC of the hippocampus with several DMN regions (Andrews-Hanna et al., 2009). Providing additional support, a meta-analysis of PET and fMRI studies of autobiographical memory created a composite activation map and revealed activity in a network of regions strongly reminiscent of the DMN (Svoboda, McKinnon, & Levine, 2006). Furthermore, episodic memory is important not just for autobiographical remembering but also in creating "mental simulations" as when one imagines the future, another proposed function of the DMN (Andrews-Hanna et al., 2010; Buckner et al., 2008; Hassabis et al., 2007; Klein, Loftus, & Kihlstrom, 2002; Schacter & Addis, 2009; Schacter et al., 2007; Stark & Squire, 2001). One study by Addis and colleagues (2007) gave participants words (e.g., dress) and asked them to imagine a scene in the foreseeable future that included the cue. Results revealed activations in regions of the DMN when participants were imagining the future (Addis, Wong, & Schacter, 2007).

Tasks requiring participants to utilize theory of mind, or the ability to take the perspective of another to infer their thoughts, have also been found to activate the DMN, particularly the medial prefrontal subsystem, which is known to be involved in self-referential and social and emotional cognition (Buckner et al., 2008; D'Argembeau et al., 2005; Gilbert et al., 2006; Gusnard et al., 2001; Macrae et al., 2004; Mitchell et al., 2002; 2006; Schilbach et al., 2008; Spreng et al., 2009). For instance, one study gave

participants a short story and asked them to infer the thoughts of a character in the story (Saxe & Kanwisher, 2003). They compared this task to one asking what would be contained in a photograph taken from a camera, in other words, requiring participants to imagine a perspective different from their own but not imagine another's thoughts. The comparison of these two tasks revealed that the former activated the DMN, while the latter did not, implying a specific role for the DMN in inferring another's *thoughts* (Saxe & Kanwisher, 2003). Subsequent studies investigated whether inferring another person's bodily sensations (e.g., being cold) would activate the DMN, but this study also supported the specificity of DMN activation for inferring others' thoughts (Saxe & Powell, 2006). Activation in the DMN has also been reported in tasks more generally related to self-relevant information, such as ascribing qualities to oneself or a close other (Goldberg et al., 2006; Grigg & Grady, 2010; Kelley, Macrae, Wyland, Caglar, Inati, & Heatherton, 2002; Schneider et al., 2008).

While delineating specific tasks that activate the DMN can promote a fuller understanding of its adaptive function, focus on task specifics instead of the commonalities across these tasks can detract from a broader conception of DMN function (Laird et al., 2009). As Buckner and colleagues argue, one aspect these three diverse activities, autobiographical remembering, imagining the future, and theory of mind, have in common is the ability to imagine a self-relevant scenario other than the present (Buckner et al., 2008). According to these authors as well as others (Bar, 2007; Hassabis & Maguire, 2007; Raichle, 2006), it is this presumed function of the DMN that enables one to engage in the adaptive skill of anticipating and predicting future events.

Presumably, this adaptive function of the DMN may have through evolutionary processes led to its seeming ubiquity in healthy human beings and primates (Buckner et al., 2008). Other authors instead focus on self-relevant information as the common link among the tasks that preferentially activate DMN regions (D'Argembeau et al., 2005; Grigg & Grady, 2010; Gusnard et al., 2001; Wicker et al., 2003). These authors emphasize that DMN activity, and hence processing information relevant to the self, dominates neural functioning when an individual is not engaged in an external task. Although the broader adaptive significance of the DMN remains to be fully elucidated, it is nevertheless important to recognize the degree of support for the DMN's involvement in internally-focused thought cited in the literature.

Despite the mounting evidence for the involvement of the DMN in internally-oriented thought, some studies have suggested the opposite: that the DMN is involved in broad, externally focused attention and its activity is attenuated during tasks requiring focused attention (Ghatan et al., 1995; Gilbert et al., 2006, 2007; Gusnard & Raichle, 2001; Laird et al., 2009; Shulman et al., 1997). Proponents of this theory argue that increases in DMN function during experiences of SITs are not due to the thought itself, but instead to the person's lack of focused attention on the task at hand, allowing such mind-wandering to occur due to a broader attentional monitoring of the environment (Gilbert et al., 2007). In support for this hypothesis, one study by Hahn and colleagues (2007) found a correlation between DMN activity and speed of responses in a target-detection task, but only when the task required broad, instead of focused, attention (Hahn, Ross, & Stein, 2007). Moreover, task-induced deactivations of the DMN are strongest in

tasks requiring focused visual attention (Shulman et al., 1997). One meta-analysis of task-related studies of the DMN found that DMN activity increased most in tasks requiring perception of external cues and introspective monitoring (Laird et al., 2009). Lesion studies also provide evidence for the DMN's role in broad external attention (Buckner et al., 2008). Humans with lesions in precuneus and cuneus, brain regions closely related to the PCC and potentially involved in the DMN, produce Balint's syndrome. Individuals with Balint's syndrome can only perceive the small part of the external world they are focusing on at a given time, often missing stimuli outside of their area of attention (Mesulam, 2000). This is the type of deficit one might expect if the DMN were indeed involved in broad attention to the external world (Buckner et al., 2008).

Differentiating between these two opposing hypotheses regarding DMN function has been difficult because internal mentation and external attention are usually confounded. However, a recent study by Andrews-Hanna and colleagues (2009) directly tested whether the DMN was involved in spontaneous cognition or broad external attention. The authors used three tasks to disentangle spontaneous cognition from external attention: two tasks meant to promote external attention required participants to detect brief flickers in peripheral (broad attention task) or central (focal attention task) locations, while a third task meant to encourage spontaneous cognitions required participants to passively look at a crosshair. A behavioral pilot study conducted by the authors validated their assumption that the tasks promoted either externally focused attention or spontaneous cognition. Results supported the role of the DMN in

spontaneous cognition; comparing the passive fixation task with both external attention tasks revealed increased activity in the DMN, with no difference in DMN activity between broad and focused attention tasks (Andrews-Hanna et al., 2009). Regions that showed increased activity in the broad versus focal attention task were those involved in visual perception and not the DMN, suggesting that the DMN is not involved in broad externally focused attention.

However, other studies attempting to differentiate between these two theories have produced conflicting results. Stawarczyk and colleagues (2011) sampled participants' thoughts during a go/no-go task and divided them into four categories: task related and stimulus dependent (thoughts completely focused on task), task related and stimulus independent (thoughts related to task but not current stimulus), task unrelated and stimulus dependent (thoughts about external stimuli but not related to the task), and task unrelated and stimulus independent (mind-wandering completely unrelated to external task). They found that DMN hub regions (PCC and ventromedial prefrontal cortex) were most active during mind-wandering and least active during thoughts completely focused on the task. However, they were active at an intermediate level during task related/stimulus independent and task unrelated/stimulus dependent thoughts. The authors interpreted these findings as evidence that the DMN may be sensitive to both internal, task unrelated thoughts, as well as external events not directly related to task performance (Stawarczyk et al., 2011). They suggest that the two opposing theories of DMN function may not be mutually exclusive, and DMN activity may vary on a

continuum from completely task unrelated to task related cognitions, according to how self-relevant the cognitions are.

Knowledge of the essential brain regions in the DMN may provide insight into its function. Related research has revealed that an important aspect of the DMN, and indeed of all functional networks, is the existence of a small number of network “hubs,” brain regions vital for coordinating the activity of other regions and subsystems in the network (Buckner et al., 2008). Buckner and colleagues (2008) identified DMN hubs by estimating the functional connectivity for three distinct regions involved in the DMN: the hippocampal formation, dorsomedial prefrontal cortex, and ventromedial prefrontal cortex. The authors took the three resulting correlation maps and identified areas of overlap, or brain regions that were functionally connected to all of the three seed regions. Three “hubs” were identified in this way: posterior cingulate cortex (PCC), ventromedial prefrontal cortex, and inferior parietal lobule (Buckner et al., 2008). Such network hubs, on which connections from spatially distributed brain regions converge, allow the coordination of distinct subnetworks within the DMN whose components may not be connected with components of other subnetworks except indirectly through the network hubs (Buckner et al., 2008). The importance of indirect structural connections among DMN regions through network hubs further elucidates the lack of perfect correspondence between structural and functional connectivity discussed previously.

These findings also highlight two of the regions most often cited as hubs in the DMN, the posterior cingulate cortex (PCC) and the medial prefrontal cortex (Andrews-Hanna et al., 2010; Stawarczyk et al., 2011; Uddin et al., 2009). These hubs are thought

to be intricately connected to adjacent regions which form subsystems within the DMN. As such, the PCC is thought to be the hub for the autobiographical memory subsystem of the DMN, while the medial prefrontal cortex is thought to be the hub for the self-referential and affective social cognition subsystem of the DMN (Amodio & Frith, 2006; Andrews-Hanna et al., 2010; Buckner & Carroll, 2007; D'Argembeau et al., 2005; Gusnard et al., 2001; Kjaer et al., 2004; Ries et al., 2006; Schneider et al., 2008; Stawarczyk et al., 2011; Uddin et al., 2010). While many of the regions comprising each of these distinct subsystems may not have strong interconnections, they are allowed to work in concert within the DMN through the interaction of their hubs (Andrews-Hanna et al., 2010; Uddin et al., 2010). From a somewhat new perspective on DMN structure, Andrews-Hanna and colleagues suggested that the primary DMN hubs, the PCC and medial prefrontal cortex, form a DMN core and are strongly connected with all other regions comprising the DMN subsystems, instead of being segregated within the subsystems themselves (Andrews-Hanna et al., 2010). Their study again demonstrated the presence of the two DMN subsystems, centered in the medial temporal lobe and ventromedial prefrontal cortex, that are involved in memory-based scene construction and self-referential and affective cognition, respectively. The DMN core exhibited the broadest range of activity among the DMN regions, being activated during both types of tasks that coincide with the DMN subsystems, while most responsive to any self-relevant cognition (Andrews-Hanna et al., 2010).

The most frequently studied DMN hub is the posterior cingulate cortex (PCC). The PCC is paralimbic cortex found in the posteromedial portion of the brain along the

posterior region of the cingulate gyrus (Mesulam, 2000). It is proximal to two other regions, retrosplenial cortex and precuneus, which are both structurally and functionally connected to PCC and, particularly in the case of retrosplenial cortex, appear to be involved in the DMN (Buckner et al., 2008; Cauda, Geminiani, D'Agata, Sacco, Duca, Bagshaw, & Cavanna, 2010; Mesulam, 2000; Zhang & Li, 2012). An image of the PCC, depicted in red, is shown in Figure 3 below. This image also illustrates the interconnections of the PCC with other regions in the DMN, namely the medial prefrontal cortex in yellow, and the medial temporal lobes, including the hippocampus, in pink and green.

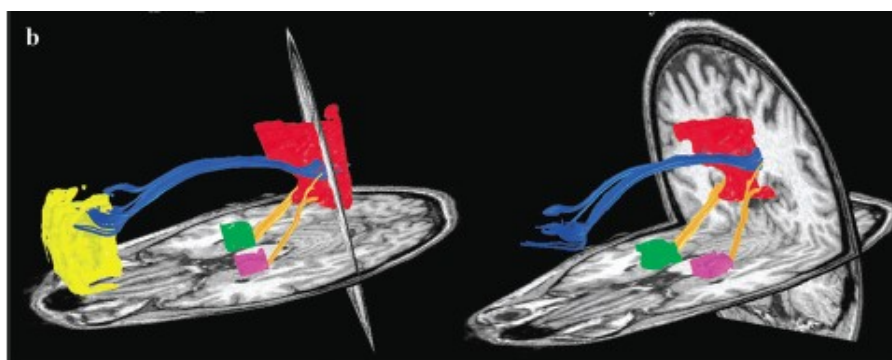


Figure 3. Diffusion tensor image of the PCC, shown in red (Greicius, Supekar, Menon, & Dougherty, 2009).

Studies of the PCC have implicated that it can be further divided into two functionally distinct dorsal and ventral subregions (Cauda et al., 2010; Vogt, Vogt, & Laureys, 2006). While the dorsal PCC appears more involved in orienting the body in space and is connected with motor regions, the ventral PCC and adjacent retrosplenial cortex are important for episodic memory and processing of self-relevant information (Cauda et al., 2010; Vogt et al., 2006). In studies in macaque monkeys, the PCC is strongly connected to the medial temporal lobe, prefrontal and medial frontal cortex, and

a monkey homologue for human inferior parietal lobule, important posterior regions in the human DMN (Buckner et al., 2008; Vogt et al., 2006).

In a recent study by Buckner and colleagues (2009), the topography of cortical hubs were mapped in a large sample of adults and implicated the PCC as a primary hub integrating posterior and anterior midline structures, with the highest degree of local and distributed connectivity. Other studies using graph theory have also implicated the PCC as one of the most pivotal cortical hubs throughout the brain which displays optimal processing efficiency (Gong et al., 2009; Gong, He, Concha, Leble, Gross, Evans, & Beaulieu, 2009; Hagmann, Cammoun, Gigandet, Meuli, Honey, Wedeen, & Sporns, 2008). Therefore, the PCC is an important DMN region in that it exhibits strong local connections with other posterior DMN regions involved in the episodic memory DMN subsystem, but also shows strong distributed connections with the anterior DMN subsystem. Many other studies have also implicated the PCC as the primary hub of the DMN (Deshpande, Santhanam, & Hu, 2011; Greicius et al., 2003, 2009; Hagmann et al., 2008; Laird et al., 2009; Margulies, Kelly, Uddin, Biswal, Castellanos, & Milham, 2007; Margulies et al., 2009; Moussa et al., 2011). Interestingly, the PCC is also the most metabolically active region throughout the brain during resting states (Andreasen et al., 1995; Cauda et al., 2010; Maquet, Degueldre, Delfiore, Aerts, Peters, Luxen, & Frank, 1997; Minoshima, Giordani, Berent, Frey, Foster, & Kuhl, 1997), by some estimates consuming 40% more glucose than the average hemispheric glucose consumption (Raichle et al., 2001), a fact further attesting to the PCC's importance in the DMN. Because of the prominent role of the PCC in integrating the subsystems of the DMN, FC

studies of the DMN often use the PCC as a seed region in FC analyses. Although the resulting FC map delineates the connectivity of the PCC, because of the high level of interconnectivity of the PCC with all other regions in the DMN, the FC map of the PCC is a very close approximation of the DMN as a whole (Greicius et al., 2003).

Posterior Cingulate Cortex Functional Connectivity and Cognition in Aging

With a deepening understanding of functional connectivity and functional networks, the field has begun to consider the relevance of functional connectivity for health and disease. An area of great interest has been changes in resting state functional connectivity with advanced age. Importantly, old age is often associated with cognitive decline, even in the absence of dementia or neurological disease (Andrews-Hanna et al., 2007; Light, 1991; Lindenberger & Baltes, 1997; Nilsson, 2003; Park et al., 1996, 2002; Schaie & Willis, 1993; Steinerman et al., 2010). Several theories posit that aging-related cognitive decline results from a disruption in functional connectivity (FC) of neural networks important for cognition, including the DMN (Andrews-Hanna et al., 2007; Buckner et al., 2005; O'Sullivan, Jones, Summers, Morris, Williams, & Markus, 2001; Palop, Chin, & Mucke, 2006). In support of such theories and the presumed importance of the DMN for maintaining cognitive health, several studies have found evidence for disruption of posterior cingulate cortex (PCC) FC in advancing age (Andrews-Hanna et al., 2007; Buckner et al., 2009; Damoiseaux et al., 2008; Esposito et al., 2008; Grady et al., 2010; Hedden et al., 2009; Koch et al., 2010; Park et al., 2010; Sambataro et al., 2010; Wang et al., 2010; Wu et al., 2007; Ystad et al., 2010).

In fact, Gong and colleagues (2009) demonstrated in whole-brain analyses using graph theory that the PCC is the most severely disrupted cortical hub across functional networks with age (Gong et al., 2009). Other fMRI research examining task-related activations and deactivations have also suggested that the PCC and surrounding areas are especially sensitive to the effects of aging (Duverne et al., 2009; Lustig et al., 2003; Miller et al., 2008; Persson et al., 2007; Wang, Kruggel, & Rugg, 2009). While the PCC is often less functionally connected as adults age, studies have also demonstrated that the medial prefrontal DMN hub may actually become more functionally connected in older age (Park et al., 2010). Some have suggested that this increase in medial prefrontal DMN connectivity may be a compensatory process in reaction to PCC disruption (Park et al., 2010). Andrews-Hanna and colleagues also found older adults to have reduced FC among DMN regions compared to younger adults during a semantic classification task, with the most robust effects occurring between anterior and posterior midline DMN regions, namely medial prefrontal cortex and PCC (Andrews-Hanna et al., 2007). While these findings remained after controlling for task performance, reduced FC between the medial prefrontal cortex and PCC in old age was strongly related to cognitive performance on tasks of memory, executive functioning, and processing speed, suggesting the importance of FC among anterior and posterior midline DMN regions for optimal cognitive performance (Andrews-Hanna et al., 2007).

Indeed, several studies have found associations between decreased FC in older adults and impaired cognitive performance, including motor control, executive functioning, processing speed, and episodic memory (Andrews-Hanna et al., 2007; Chen

et al., 2009; Damoiseaux et al., 2008; Persson et al., 2007; Sambataro et al., 2010; Wang et al., 2010; Wu et al., 2007). Because aging is often associated with episodic memory decline, many studies have sought neural bases for these memory declines through functional imaging and connectivity research with older adults (e.g., Bender, Naveh-Benjamin, & Raz, 2010; Grady, 2000; Grady & Craik, 2000; Head, Rodrigue, Kennedy, & Raz, 2008; Nilsson, 2003). Episodic memory is conscious memory for events which can be spontaneously recalled along with the time and place of their occurrence (Mesulam, 2000). Episodic memory is traditionally thought to rely on medial temporal lobe structures including the hippocampus and surrounding areas (e.g., entorhinal cortex and parahippocampal gyrus; Mesulam, 2000; Milner, Corkin, & Teuber, 1968; Squire, 1992). However, episodic memory also relies on the interaction of medial temporal structures with more distributed regions throughout the brain (Mesulam, 2000). Indeed, much research has focused exclusively on the importance of PCC FC for episodic memory in aging because of the PCC's close relationship with medial temporal lobe regions underlying episodic memory as well as the role of the DMN in autobiographical memory, a subcategory of episodic memory (Damoiseaux & Greicius, 2009; Dickerson & Sperling, 2009; Kahn, Andrews-Hanna, Vincent, Snyder, & Buckner, 2008). As described earlier, several studies, including meta-analyses, have revealed significant overlap between the neural network associated with autobiographical episodic memory and the DMN (Ino, Nakai, Azuma, Kimura, & Fukuyama, 2011; Spreng & Grady, 2009; Spreng et al., 2009; Svoboda et al., 2006; Wang et al., 2009). In fact, one study examining brain regions that were preferentially active during autobiographical memory

while also being less active during other tasks found that the PCC was the DMN region most closely associated with autobiographical memory (Ino et al., 2011), a finding echoed by others in the literature as well (Summerfield, Hassabis, & Maguire, 2009).

Functional connectivity studies in aging have also revealed the importance of PCC FC for intact memory performance. He and colleagues (2012) correlated older adults' resting functional connectivity with their performance on two verbal list learning tasks. They were specifically interested in the relative contribution of DMN functional connectivity, gray matter volume, and white matter hyperintensities on memory performance. After creating an average DMN map by overlapping FC maps created with each individual DMN hub (i.e., PCC, medial prefrontal cortex, and inferior parietal cortex), they found that increased DMN connectivity, particularly between medial prefrontal cortex and left inferior parietal cortex, predicted better memory performance. This effect was most pronounced in participants exhibiting gray matter atrophy, suggesting that preserved DMN functional connectivity may be especially important to maintaining episodic memory performance in the face of neural abnormalities (He et al., 2012). Wang et al. (2010) also explored the effect of PCC functional connectivity on memory performance in older adults, although they focused specifically on the connectivity between the PCC and the hippocampus. In their study, they gathered resting-state fMRI data from a group of older adults before they performed an associative memory task in the scanner. Increased connectivity between the PCC and hippocampus predicted better subsequent memory performance. Moreover, PCC-hippocampal connectivity also predicted better memory performance on neuropsychological measures,

although it was not related to performance in any other cognitive domains (Wang et al., 2010). While it remains unclear whether it is overall PCC connectivity or connectivity of PCC to specific brain regions that has a greater impact on memory performance, the dependence of intact memory performance on the ability of the PCC to coherently interact with spatially distributed neural regions has been consistently demonstrated.

Although episodic memory is often referred to as a unified cognitive domain, it is actually composed of several distinct memory-related processes, including encoding into short- and long-term memory, storage in long-term memory, and retrieval from long-term memory for conscious recall of the to-be-remembered information. Interestingly, studies have suggested that the DMN may play an important role during episodic memory retrieval, but not encoding (Daselaar, Prince, Dennis, Hayes, Kim, & Cabeza, 2009; Henson, Hornberger, & Rugg, 2005; Huijbers, Pennartz, Cabeza, & Daselaar, 2011; Kao, Davis, & Gabrieli, 2005; Kim et al., 2009; Miller et al., 2008; Otten & Rugg, 2001; Prince, Daselaar, & Cabeza, 2005; Shrager, Kirwan, & Squire, 2008; Vannini, O'Brien, O'Keefe, Pihlajamäki, LaViolette, & Sperling, 2011; Wagner, Shannon, Kahn, & Buckner, 2005; Weis, Klaver, Reul, Elger, & Fernandez, 2004). For instance, Daselaar and colleagues (2009) examined the association of activity in the DMN regions of the posterior midline region (i.e., PCC) and lateral posterior parietal cortex during episodic memory encoding and retrieval with subsequent memory for the learned items. They found, across five different fMRI memory tasks, that activity of these regions during retrieval predicted better memory performance, while activity of these regions during encoding predicted poorer subsequent memory performance (Daselaar et al., 2009).

Furthermore, they demonstrated that the regions showing increased activity during memory retrieval compared to encoding were also those that typically deactivated during tasks while being more active at rest (i.e., DMN regions). It is noteworthy that the DMN's apparent role in episodic retrieval coincides with its proposed functions in constructing mental scenes based on episodic memory (Daselaar et al., 2009). The association of DMN activity with impaired memory encoding also concurs with the notion of memory encoding failure being due to inability to inhibit task-irrelevant activity during encoding (Stevens, Hasher, Chiew, & Grady, 2008).

Two theories have been proposed for the DMN's seemingly exclusive role in episodic memory retrieval. One is that this specificity is related to the internal (i.e., memory retrieval) over external (i.e., memory encoding) attentional preference of the DMN (Huijbers et al., 2011). In other words, according to this theory, when one is engaged in episodic memory encoding, attention is focused on the externally presented stimulus to be remembered, hence leading to a deactivation of DMN regions. In contrast, during episodic memory retrieval, one's attention is focused inward on identifying the correct memory trace of the learned item, mediated by increased DMN activity. Another theory is that the hippocampus, a medial temporal lobe structure important for memory, is coupled with the DMN differently across memory encoding and retrieval (Huijbers et al., 2011). This theory proposes that the DMN is coupled with the hippocampus during memory retrieval, such that in this case DMN and hippocampal activity work in concert to successfully retrieve memory traces from memory stores. In contrast, the DMN is proposed to be uncoupled with the hippocampus during memory encoding, so that DMN

activity at this time is competing with the hippocampal activity driving memory encoding. Huijbers and colleagues (2011) designed a study to test these hypotheses and found support for the hippocampal coupling hypothesis. While DMN activity was associated with memory retrieval instead of encoding, it was not modulated by whether the activity was internal versus external. Importantly, the hippocampus was functionally coupled (i.e., showed the same pattern of activity to memory performance) to the DMN during memory retrieval but not memory encoding, suggesting this coupling as the source of associations of DMN activity with better memory retrieval (Huijbers et al., 2011). In support, other studies have also reported better memory performance with increased functional connectivity of DMN regions, especially the PCC, with the hippocampus (Ranganath, Heller, Cohen, Brozinsky, & Rissman, 2005).

Beyond findings with non-demented older adults, research with patient populations have also demonstrated the importance of PCC FC for maintaining episodic memory performance (Greicius et al., 2004; Wang et al., 2006; 2007; Wu et al., 2007). Greicius and colleagues (2004) examined the resting-state functional connectivity of cognitively intact older adults and older adults with Alzheimer's disease (AD) using independent components analysis while they performed a sensory-motor processing task. They found that PCC and hippocampal connectivity was significantly reduced in AD patients compared to cognitively normal older adults, suggesting that it may play a role in the prominent memory impairments exhibited in these patients as well as the common finding of reduced PCC metabolism in AD (Greicius et al., 2004; Johnson, Jones, Holman, Becker, Spiers, Satlin, & Albert, 1998; Matsuda, 2001; Minoshima et al., 1997).

Other studies have also reported reductions in PCC FC in AD (Wang et al., 2006; 2007; Wu et al., 2011) and mild cognitive impairment, a risk factor for dementia.

However, not all studies have found changes in DMN activity with age. Beason-Held and colleagues (2009) used PET imaging in a longitudinal study of older adults at rest and during memory recognition tasks (Beason-Held, Kraut, & Resnick, 2009). When comparing rest activity to activity during task performance to isolate areas showing rest-related activity changes, the authors found no changes in activity in DMN regions including the medial prefrontal cortex, PCC, and hippocampus, across an eight-year span of time. However, they did find longitudinal activity changes in some regions not typically associated with the DMN in younger adults, including superior frontal, medial insula, parahippocampal, and middle occipital gyri. They suggest that minimal changes in DMN activity may occur in advanced healthy aging, although changes beyond regions typically associated with the DMN may be found. A second study by Wang and colleagues (2009) reported similar results when comparing two groups of older adults in the sixth and ninth decades of their lives during an episodic memory task. The authors reported few differences in activation patterns between the two groups despite differences in task performance, suggesting that age related changes in neural activation patterns may plateau in old-old age. However, one interesting finding was that the young-old adults over-recruited the medial parietal areas including the PCC compared to the old-old adults, which the authors suggest may reflect compensatory processes in the young-old group that become impaired with advancing age. As such, the posterior medial cortices may be especially sensitive to the effects of advancing age (Wang et al., 2009).

Importantly, these studies' emphasis on changes in regional activity levels and lack of examination of functional connectivity among brain regions may explain their different pattern of findings compared to other studies reporting age-related differences in FC with advancing age. Perhaps, while DMN regions do not show overt changes in activity levels over time, the correlation of activity among these regions does change, suggesting reductions in network coherence despite maintenance of average regional activity levels.

Abnormal functional connectivity and altered DMN activity in older adults has been cited both at rest and during task performance (Andrews-Hanna et al., 2007). A consistent finding in older adults is the significant reduction in task-induced deactivations of the DMN. In other words, whereas healthy younger adults typically show reduced activity in the DMN in a variety of tasks, older adults do not, instead showing relatively higher levels of activity in the DMN during task performance (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008; Duvernoe et al., 2009; Esposito et al., 2008; Grady et al., 2006; Grady et al., 2010; Koch et al., 2010; Lustig et al., 2003; Miller et al., 2008; Park et al., 2010; Persson et al., 2007; Sambataro et al., 2010). Andrews-Hanna and colleagues (2007) examined functional connectivity in the DMN in younger and older adults during a semantic classification task. They found that older adults showed significantly higher activity in medial prefrontal cortex and PCC DMN regions than younger adults during task performance. Furthermore, increased activity in these DMN regions was significantly associated with reduced FC among them. While their results are correlational and cannot reveal the direction of causality, they suggest that disruption in

task-reduced deactivations in older adults is significantly associated with disruptions in functional connectivity (Andrews-Hanna et al., 2007).

Several theories have been proposed to explain disruptions in task-induced deactivation in old age. An early proposal suggests that age-associated reductions in task-induced deactivations are due to compensatory processes in older adults (Andrews-Hanna et al., 2007). According to this theory, older adults recruit additional brain regions, predominantly in the frontal lobes, than younger adults during task performance to compensate for reduced neural integrity, including gray matter atrophy and white matter disruption (Goh & Park, 2009; Park & Reuter-Lorenz, 2009; Raz et al., 2005). Thus, increased DMN activity during task performance, particularly in frontal regions, may represent an attempt to maintain task performance in the face of a higher level of neural abnormality (Grady & Craik, 2000; Reuter-Lorenz, Marshuetz, Jonides, Smith, Hartley, & Koeppel, 2001). Because older adults need to recruit additional regions to accomplish the same tasks and younger adults, some argue that this supposed compensatory response is actually a marker of reduced neuronal efficiency and a sign of dedifferentiation of brain regions with age (Goh, 2011). Studies with older adults have shown that posterior regions, including the PCC, become less specific in their responding to stimuli, along with a stronger recruitment of anterior regions to stimuli not normally associated with their activity in younger age groups (Goh, 2011). However, St-Laurent and colleagues (2011) demonstrated that older adults' tendency toward less differentiated neural responding is not the case across all cognitive tasks (St-Laurent, Abdi, Burianova, & Grady, 2011). The authors examined older and younger adults' fMRI activity during

episodic and semantic memory tasks. They found that while older adults showed preserved activity in a core memory retrieval network also activated in younger adults, older adults showed less selective activity in other regions associated with episodic memory.

Observations of age-related decreases in functional differentiation of brain regions are also consistent with the hemispheric asymmetry reduction in older adults (HAROLD) model (Cabeza, 2002). The foundation of the HAROLD model lies in the common finding of reduced lateralization and hemispheric asymmetry in task-related activity with age (Cabeza, Daselaar, Dolcos, Prince, Budde, & Nyberg, 2004; Cabeza, Grady, Nyberg, McIntosh, Tulving, Kapur, et al., 1997; Cabeza et al., 2002; Dennis, Daselaar, & Cabeza, 2007; Duverne et al., 2009; Grady, McIntosh, & Craik, 2005; Madden, Turkington, Provenzale, Denny, Hawk, Gottlob, & Coleman, 1999; Morcom, Good, Frackowiak, & Rugg, 2003; Reuter-Lorenz, Jonides, Smith, Hartley, Miller, Marshuetz, & Koeppel, 2000). Based on the association of increased bilateral activity with better task performance, age-related reduction in laterality described by the HAROLD model is conceptualized by some as a compensatory response to maintain task performance in the face of increased neural abnormalities (Cabeza et al., 2002). However, others conceptualize reductions in hemispheric specialization as a pathological process, perhaps related to deficits in transcallosal inhibition between the hemispheres (Logan, Sanders, Snyder, Morris, & Buckner, 2002). Relatedly, Li and colleagues (2009) demonstrated that reductions in hemispheric asymmetry during a verbal working memory task were associated with relatively reduced FC in the right hemisphere, demonstrating

that functional connectivity can indeed have an impact on dedifferentiation in the aging brain (Li, Moore, Tyner, & Hu, 2009). An interesting pattern of findings related to the compensatory and dedifferentiation hypotheses is the fact that older adults typically show different regions involved in the DMN than those seen in younger ages, such as orbital and inferior frontal, parahippocampal, and lateral temporal structures (Beason-Held et al., 2009; Greicius et al., 2004; Meunier, Achard, Morcom, & Bullmore, 2009). For instance, Grady and colleagues found that, during rest as compared to cognitive tasks, younger adults had more extensive posterior DMN activity, while older adults had more extensive frontal DMN activity (Grady et al., 2010). These findings concur with both the notion of dedifferentiation as well as that advanced age is associated with increased reliance on frontal regions, perhaps as part of a compensatory process (Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008).

Neural dedifferentiation has also been detected in older adults' task performance, such that older adults have difficulty making fine-grained perceptual distinctions than their younger counterparts after controlling for changes in visual acuity (Lindenberger, Scherer, & Baltes, 2001; Toner, Pirogovsky, Kirwan, & Gilbert, 2009). Reductions in processing specificity also appear in older adults' episodic memory performance (Bender et al., 2010; Goh, 2011). While healthy older adults maintain the ability to recognize previously studied material, they have difficulty recalling characteristics associated with the studied material (e.g., where it was studied, the font words were studied in; Bender et al., 2010; Chalfonte & Johnson, 1996; Henkel, Johnson, & De Leonardis, 1998; Naveh-Benjamin, 2000; Naveh-Benjamin & Craik, 1995, 1996; Naveh-Benjamin, Guez, Kilb, &

Reedy, 2004; Old & Naveh-Benjamin, 2008; Ronnlund, Nyberg, Backman, & Nilsson, 2005). More broadly, older adults have been found to use more gist- and familiarity-based memory encoding strategies than younger adults, leading them to make errors in recognition of items which have fine-grained distinctions among them (Hay & Jacoby, 1999; Howard, Bessette-Symons, Zhang, & Hoyer, 2006; Koutstaal & Schacter, 1997; Prull, Dawes, Martin, Rosenberg, & Light, 2006; Stark, Yassa, & Stark, 2010; Yonelinas, 2002). Interestingly, research has suggested that DMN activity is associated with frank recall instead of recognition of learned items (Kim, 2010). It may therefore be the disruption of DMN connectivity in older age, and associated declines in overt recall of learned material, that produces older adults' increased reliance on familiarity-based memory strategies. Thus, as Goh (2011) discusses, disruptions in older adults' functional connectivity across widely distributed brain regions may drive dedifferentiation and compensatory recruitment, which then impact older adults' behavioral performance on tasks requiring associative memory of specific contextual information.

Although there is much research suggesting neural dedifferentiation in older adults may reflect compensatory processes, the frequent association of reduced DMN deactivation with *poorer* task performance, especially in posterior DMN regions, suggests that these findings may not be solely related to compensatory processes. A second theory purports that older adults show higher activity in DMN regions during task performance due to an impaired ability to efficiently shift neural resources from the default-mode to task-positive networks (Grady et al., 2006; Grady et al., 2010; Lustig et al., 2003; Persson et al., 2007). Whereas young adults are able to flexibly switch neural

resources from processing in the DMN at rest to processing in task-positive networks during goal-directed activity, older adults are less able to flexibly allocate neural resources, leading to increased DMN activity during tasks and concomitant reductions in task performance (Clapp et al., 2011; Park et al., 2010). Indeed, studies have shown that the degree of the inverse relationship between DMN and task-positive network activity is associated with improved task performance (e.g., Kelly, Uddin, Biswal, Castellanos, & Milham, 2008; Park et al., 2010; Wig, Grafton, Demos, Wolford, Petersen, & Kelley, 2009). Studies have also consistently reported a positive relationship between DMN deactivation and task difficulty, implying that performance on particularly difficult tasks requires more neural resources be shifted from the DMN to task-positive networks (McKiernan et al., 2003; Park et al., 2010; Persson et al., 2007). Thus, the balance between activity in the default mode and task positive networks, presumably mediated by the ability to shift neural resources between them, may be crucial for optimal cognitive performance and may degrade in old age (Grady et al., 2010).

A recent study by Grady and colleagues (2010) provided evidence demonstrating the complementary relationship between the compensatory and shifting of neural resources hypotheses of reduced task-related DMN deactivations in older adults. The study included samples of younger and older adults who underwent fMRI during rest and a variety of cognitive tasks. Interestingly, although older adults demonstrated a restricted area of frontal expansion of DMN regions, increasing age was generally associated with *shrinkage* in the extent of the DMN and overall reduction in DMN connectivity. This DMN shrinkage was associated with increased task-related activity in several DMN

regions in older adults as well as a tendency to over-recruit regions in the task-positive network (TPN) during task performance. While increased task-related DMN activity and over-recruitment of TPN regions were generally associated with poorer performance, increased task-related recruitment of dorsolateral prefrontal regions in older adults facilitated performance. Thus, these results demonstrate that aging is associated with a reduction in task-induced DMN deactivations, shrinkage of the DMN, and expansion of the TPN to facilitate task performance (Grady et al., 2010). The authors suggested that both the shrinkage and functional disruption of the DMN may attenuate older adults' abilities to deactivate the DMN during tasks, requiring the increased activity of TPN regions to maintain cognitive performance.

Mechanisms for Functional Connectivity Disruption in Aging

On a broader level, mechanisms driving the disruption of functional networks with aging remain to be fully elucidated. There are several reasons large-scale neural networks may become disrupted in aging, including gray matter atrophy, changes in neurotransmitter activity and neuronal plasticity, accumulation of neuronal protein abnormalities (e.g., beta amyloid), and alterations in the white matter connections between brain regions in the network (Chen et al., 2009; Goh, 2011; Head, Buckner, Shimony, Williams, Akbudak, Conturo, et al., 2004; Hedden et al., 2009; Li et al., 2009; O'Sullivan et al., 2001; Pfefferbaum, Adalsteinsson, & Sullivan, 2005; Pfefferbaum, Sullivan, Hedehus, Lim, Adalsteinsson, & Moseley, 2000; Salat, Tuch, Greve, van der Kouwe, Hevelone, Zaleta, et al., 2005; Sullivan & Pfefferbaum, 2006). It is well-established that aging is associated with reductions in gray matter volume, particularly in

frontal, parietal, and medial temporal regions (Allen, Bruss, Brown, & Damasio, 2005; Head, Kennedy, Rodrigue, & Raz, 2009; Head et al., 2008; Raz, Gunning-Dixon, Head, Dupuis, & Acker, 1998; Raz et al., 2005; Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003; Rodrigue & Raz, 2004; Salthouse, 2011; Scahill, Frost, Jenkins, Whitwell, Rossor, & Fox, 2003; Walhovd, Fjell, Reinvang, Lundervold, Dale, Eileersten, et al., 2005). Such gray matter atrophy in turn often coincides with cognitive decline (see Salthouse, 2011, for a review). Furthermore, gray matter atrophy is closely correlated across spatially distributed regions within a functional network, suggesting that degenerative processes similarly impact functionally correlated regions despite considerable physical distance between them (Seeley et al., 2009). Protein-mediated neuronal abnormalities (e.g., beta amyloid), which are linked to Alzheimer's disease and tend to originate in posterior and medial temporal DMN hubs, have also been associated with reduced functional connectivity in older adults (e.g., Buckner et al., 2005; Hedden et al., 2009; Mormino, Smiljic, Hayenga, Onami, Greicius, Rabinovici, et al., 2011; Sheline, Raichle, Snyder, Morris, Head, Wang, & Mintun, 2010). Thus, the apparent sensitivity of medial cortical regions to the effects of aging may be due, at least in part, to the accumulation of neuronal abnormalities during prodromal phases of Alzheimer's disease (Buckner et al., 2005).

White matter integrity is also commonly found to be disrupted in aging (Bennett, Madden, Vaidya, Howard, & Howard, 2010; Davis, Dennis, Buchler, White, Madden, & Cabeza, 2009; Head et al., 2004; Longstreth, Manolio, Arnold, Burke, Bryan, Jungreis, et al., 1996; Madden, Bennett, & Song, 2009; Madden, Spaniol, Costello, Bucur, White,

Cabeza, et al., 2009; Manolio, Kronmal, Burke, Poirier, O’Leary, Gardin, et al., 1994; Penke, Maniega, Murray, Gow, Hernandez, Clayden, et al., 2010; Persson, Nyberg, Lind, Larsson, Nilsson, Ingvar, & Buckner, 2006; Pfefferbaum et al., 2005; Pfefferbaum & Sullivan, 2003; Pfefferbaum et al., 2000; Sullivan & Pfefferbaum, 2003, 2006; Vernooij, de Groot, van der Lugt, Ikram, Krestin, Hofman, Niessen, & Breteler, 2008; Yue, Arnold, Longstreth, Elster, Jungreis, O’Leary, et al., 1997), with up to 96% of individuals over the age of 65 showing white matter abnormalities (Longstreth, Arnold, Beauchamp, et al., 2005). In fact, white matter volume peaks from 25 to 35 years, subsequently showing gradual decline into old age that some have found to outweigh age-associated gray matter atrophy (Allen et al., 2005; Bartzokis, Cummings, Sultzer, Henderson, Nuechterlein, & Mintz, 2003; Giorgio, Santelli, Tomassini, Bosnell, Smith, De Stefano, & Johansen-Berg, 2010; Guttmann, Jolesz, Kikinis, Killiany, Moss, Sandor, & Alberg, 1998; Jernigan, Archibald, Fennema-Notestine, Gamst, Stout, Bonner, & Hesselink, 2001; Resnick et al., 2003; Salat, Greve, Pacheco, Quinn, Helmer, Buckner, & Fischl, 2009; Sowell, Peterson, Thompson, Welcome, Henkenius, & Toga, 2003; Sullivan & Pfefferbaum, 2006; Tamnes, Ostby, Fjell, Westlye, Due-Tønnessen, & Walhovd, 2010). White matter volume appears to decline most precipitously in the very old and to exhibit a predilection for prefrontal regions, only spreading to posterior regions in more advanced or pathological aging, although disruption in microstructural white matter integrity occurs much earlier (Giorgio et al., 2010; Gunning-Dixon, Brickman, Cheng, & Alexopoulos, 2009; Head et al., 2004; O’Sullivan et al., 2001; Pfefferbaum & Sullivan, 2003; Raz et al., 2005; Sachdev, Wen, Chen, & Brodaty, 2007; Salat, Buckner, Snyder, Greve, Desikan, Busa, et

al., 2004; Salat, Kaye, & Janowsky, 1999; Sullivan, Adalsteinsson, Hedehus, Ju, Moseley, Lim, & Pfefferbaum, 2001). Studies suggest white matter disruption occurs in old age due to de-myelination of axonal projections, detracting from the efficiency of neural signaling mediated by the axons (Bartzokis, 2004; Goh, 2011; Gunning-Dixon et al., 2009; Peters, 2002). Indeed, one investigation based on graph theory found that, whereas the young adult brain is organized into functional networks to optimize processing efficiency, normal aging is associated with a reduction in processing efficiency due to alterations in functional networks, especially those found in frontal, temporal, and subcortical regions (Achard & Bullmore, 2007). Changes in white matter integrity may help explain reductions in neural efficiency with advancing age (Salthouse, 2011). Furthermore, although variable findings have been reported in the literature, white matter disruption in aging has frequently been associated with cognitive decline, including decline in episodic memory (Breteler, van Swieten, Bots, et al., 1994; Brickman, Zimmerman, Paul, Grieve, Tate, Cohen, et al., 2006; Bucur, Madden, Spaniol, Provenzale, Cabeza, White, & Huettel, 2008; Charlton, Shiavone, Barrick, Morris, & Markus, 2010; DeBette & Markus, 2010; Gunning-Dixon & Raz, 2000; Gunning-Dixon et al., 2009; Kennedy & Raz, 2009; Madden et al., 2009; Persson et al., 2006; Prins, van Dijk, den Heijer, Vermeer, Jolles, Koudstaal, et al., 2005; Reed, Eberling, Mungas, Weiner, Kramer, & Jagust, 2004; Salthouse, 2011; van der Flier, van Straaten, Barkhof, Verdelho, Madureira, Pantoni, et al., 2005; Vannorsdall, Waldstein, Kraut, Pearlson, & Schretlen, 2009). Therefore, white matter disruption commonly occurs in advancing age and may reduce functional connectivity by impairing the efficiency with which spatially

distributed regions communicate, producing subsequent cognitive impairment (Salthouse, 2011).

Despite the prevalence of white matter degeneration with age, the literature has only begun to consider its influence on functional connectivity. What work has been done suggests that white matter integrity is vital for maintaining functional connectivity in advancing age (Andrews-Hanna et al., 2007; Chen et al., 2009; Duong et al., 2005; Gong et al., 2009). For instance, Andrews-Hanna and colleagues (2007) found that reduced FC between medial prefrontal cortex and PCC was associated with disruption in white matter integrity within the brain. Moreover, FC findings were independent of brain abnormalities (i.e., beta amyloid) linked to Alzheimer's disease, implying a unique and important role for white matter integrity in maintaining FC. The authors suggest that FC disruptions found in normal aging, which are strongly linked to dysfunction in anterior brain regions and their disconnection from posterior structures, are distinct from FC disruptions found in Alzheimer's disease, which predominantly involve posterior and medial temporal structures important for memory (Andrews-Hanna et al., 2007; Drzezga, Becker, Van Dijk, Sreenivasan, Talukdar, Sullivan, et al., 2011; Greicius et al., 2004; Lustig et al., 2003; Rombouts, Barkhof, Goekoop, Stam, & Scheltens, 2005).

It is important to note that, although research frequently considers age-associated neurobiological mechanisms independently, they often coincide and may in fact be causally linked with one another (Appel et al., 2009; Appelman et al., 2009; Folstein & Folstein, 2010; Gorelick, Scuteri, Black, DeCarli, Greenberg, Iadecola, et al., 2011; Seeley et al., 2009). It is particularly difficult to parse apart the causal effects of each

mechanism on behavioral outcomes when they are so often confounded, and it is likely that each neurobiological change with age plays a role in the cognitive declines and alterations in functional connectivity observed in older adults (Appelman et al., 2009; Buckner et al., 2005; Gorelick et al., 2011; Seeley et al., 2009). However, investigating the role of white matter disruption in producing functional connectivity declines in aging is particularly compelling in light of the function of white matter to promote electrochemical communication among disparate brain regions. Without these white matter connections, brain regions are effectively disconnected from each other and are presumably less able to coordinate their activity as part of a coherent network (Madden et al., 2009; O'Sullivan et al., 2001).

Vascular Risk Factors and Functional Connectivity

Although it is clear that functional connectivity disruptions among older adults are related to gray and white matter changes in the brain, causal factors driving these gray and white matter changes remain a mystery. One possible antecedent for changes in gray and white matter, and ultimately for changes in DMN functional connectivity, is vascular risk, such as hypertension, diabetes, and cigarette smoking. Indeed, the high prevalence of vascular risk and disease in older adults raises the possibility that they may produce the white and gray matter changes so commonly observed in otherwise healthy aging. Vascular risk occurs in a high percentage of adult Americans, with estimates suggesting that at least 90% of middle-aged adults will have hypertension at some point in their lives (Ong et al., 2007), and over 25% of adults over the age of 65 will have diabetes (CDC, 2011). It is well-established that vascular risk and disease are associated with a variety of

white matter abnormalities in non-demented individuals, including white matter hyperintensities, lacunae, and more general white matter volume and integrity loss (Appel et al., 2009; Brickman et al., 2010; Burgmans et al., 2010; Correia, Lee, Voorn, Tate, Paul, Zhang, et al., 2008; DeCarli, Miller, Swan, Reed, Wolf, Garner, et al., 1999; de Leeuw, de Groot, Oudkerk, Witteman, Hofman, van Gijn, & Breteler, 2002; Delano-Wood, Abeles, Sacco, et al., 2008; Domino, 2008; Dufouil, Chalmers, Coskun, Besancon, Bousser, Guillon, et al., 2005; Dufouil, de Kersaint-Gilly, Besancon, Levy, Auffray, Brunnereau, et al., 2001; Gons et al., 2010; Gottesman et al., 2010; He et al., 2010; Kennedy & Raz, 2009; Knopman, Mosley, Catellier, & Sharrett, 2005; Kuller et al., 2010; Lazarus et al., 2005; Lee et al., 2010; Longstreth et al., 1996; Madden et al., 2009; Manolio et al., 1994; Murray, Staff, Shenkin, Deary, Starr, & Whalley, 2005; Raz et al., 2007; van Harten, Oosterman, Potter van Loon, Scheltens, & Weinstein, 2007). In fact, vascular factors such as hypertension have been found to spread the predominantly anterior alterations in white matter integrity observed in healthy aging to more posterior regions, including the posterior cingulate cortex (Kennedy & Raz, 2009). Moreover, vascular risk factors also produce gray matter atrophy concomitantly with white matter damage (Appelman et al., 2009; Bresser et al., 2010; Bruehl et al., 2009; Longstreth et al., 2000; van Harten et al., 2006).

Because reductions in gray and white matter integrity have been proposed as etiological factors for functional connectivity disruption, and because vascular risk impacts both gray and white matter integrity, it is reasonable to investigate the role of vascular risk in producing functional connectivity disruption in aging. As noted above,

several other empirical findings also support vascular risk as a precursor for age-related DMN functional connectivity disruptions. Vascular risk has been shown to alter cerebral metabolism, and perturbations in cerebral metabolism have been tied to reductions in functional connectivity (Kapogiannis & Mattson, 2011), providing further evidence to substantiate the causal role of vascular risk in functional connectivity disruption. Moreover, the ability of vascular risks such as hypertension to produce posterior white matter alterations also supports the notion of vascular risk as an antecedent to DMN functional connectivity disruptions. Finally, important medial nodes in the DMN, namely the anterior and posterior cingulate cortices, are involved in cerebrovascular reactivity to stress (Ryan, Sheu, & Gianaros, 2011), which has been found to be further modulated by existence of vascular pathologies and risk factors. It therefore seems plausible that vascular risk factors may alter functional connectivity of the posterior cingulate cortex, the prime node of the DMN.

However, a dearth of studies has directly explored the impact of vascular risk on functional connectivity. One of these few studies examined functional connectivity using magnetoencephalography among adults with and without type 1 diabetes (Duinkerken et al., 2009). They found that diabetics with microvascular complications had less functional connectivity than controls while diabetics without microvascular involvement actually had higher levels of functional connectivity. It may be that increased functional connectivity in diabetics without microvascular involvement represents a compensatory response, while among individuals with more complicated diabetes, the added pathology overwhelms compensatory efforts, leading to reductions in FC (Duinkerken et al., 2009).

A second study of older adults with and without type 2 diabetes demonstrated a reduction in functional connectivity of the hippocampus with several nodes in the DMN, including the posterior cingulate cortex, anterior cingulate cortex, and inferior parietal lobule, in diabetics compared to their healthy cohorts (Zhou et al., 2010). In light of the frequent association of type 2 diabetes with episodic memory impairment, which was also replicated by this study, the authors suggested that memory impairments in diabetics are mediated by a functional disconnection of the episodic memory network, which significantly overlaps with much of the DMN (Zhou et al., 2010). A final investigation by Sun and colleagues (2011) explored PCC functional connectivity in patients with subcortical ischemic vascular disease with and without cognitive impairment. They found that the group with cognitive impairment demonstrated reduced connectivity of the PCC with middle temporal gyrus, anterior cingulate, caudate, middle frontal gyrus, and paracentral lobule, while exhibiting increased connectivity of the PCC with the inferior temporal and left middle gyri, precentral gyrus, and superior parietal lobule (Sun et al., 2011). Thus, although both patient groups had vascular disease, the group with impaired cognition showed altered posterior cingulate functional connectivity, perhaps representing both pathological and compensatory processes.

Some studies in this area have addressed the issue of decreased task-induced deactivation of DMN regions during cognitive performance among those with high vascular burden. One such effort from Braskie et al. (2010) examined the impact of systolic blood pressure, body mass index (BMI), and total cholesterol on functional activations during a memory task among older adults. Interestingly, individuals with high

systolic blood pressure and BMI demonstrated increased activation in the PCC, parietal, frontal, and temporal cortices during the memory task. Increased activation in the PCC and parietal cortex was evident even among individuals with relatively higher systolic blood pressure that was still in the normal range (Braskie, Small, & Bookheimer, 2010). These results were maintained even after controlling for age, performance, and hippocampal volumes, suggesting vascular risk exerted unique influences on posterior cingulate and parietal activity. While the authors primarily conceptualized their findings in terms of a compensatory increase in brain activity to maintain task performance in the face of neuropathologic changes, the results could instead be due to impairment in task-induced deactivation of DMN regions. Similarly, Wessels and colleagues (2006) examined functional activation among patients with type 1 diabetes with and without microvascular complications. Despite equal cognitive performance, patients with microvascular complications of type 1 diabetes demonstrated impaired deactivation in DMN regions during episodes of hypoglycemia than diabetics without microvascular complications. This suggests that the severity of diabetes is important to consider when examining resultant alterations in brain functioning. That being said, these findings also demonstrate that type 1 diabetes can disrupt functional communication of neural networks (Wessels, Rombouts, Simsek, Kuijer, Kostense, Barkhof, et al., 2006).

Vascular Risk Factors and Cognition

Given the apparent relationship of vascular risk with loss of gray and white matter integrity as well as disruption of functional connectivity, it is not surprising that vascular risk also has a deleterious effect on cognition. Indeed, although cognitive decline is often

seen in “normal” aging, in light of the high frequency of vascular risk factors in old age, much of this age-associated cognitive decline is likely related to or exacerbated by vascular pathology (Hughes & Ganguli, 2009; Kalaria, 2010; Llewellyn, Lang, Xie, Huppert, Melzer, & Langa, 2008; Raz et al., 2007). In accord with this notion, a prospective clinicopathological study of older adults revealed that white matter pathology found at autopsy, including microvascular lesions and periventricular and diffuse demyelination, accounted for over 27% of cognitive variability of older adults on the Clinical Dementia Rating scale (Kovari, Gold, Herrmann, Canuto, Hof, Michel, et al., 2004). In addition, Folstein and Folstein (2010) recently suggested that the cognitive deficits commonly observed in non-demented older adults may also be due to vascular-induced brain atrophy. Beyond directly impacting gray and white matter integrity, vascular risk factors have also been thought to impact cognition through such diverse mechanisms as metabolic processes, including metabolically induced alterations in neuromodulation and pathological accumulation of intra- and extra-neuronal proteins (i.e., A β and tau), atherosclerosis and other factors leading to cerebral hypoperfusion and alterations in the blood-brain barrier, and cerebral inflammatory and oxidative processes, all of which can also indirectly affect gray and white matter integrity (Hughes & Ganguli, 2009; Kalaria, 2010; Kapogiannis & Mattson, 2011). Composite indicators of vascular risk have frequently been associated with cognitive decline and dementia (Bangen et al., 2007; 2010; Goldstein, Ashley, Endeshaw, Hanfelt, Lah, & Levey, 2008; Llewellyn et al., 2008), as have individual vascular risk factors, including smoking (Almeida, Hulse, Lawrence, et al., 2002; Anstey, von Sanden, Slim, et al., 2007; Barnes, Haight, Mehta,

Carlson, Kuller, & Tager, 2010; Collins, Sachs-Ericsson, Preacher, Sheffield, & Markides, 2009; Deary, Pattie, Taylor, et al., 2003; Durazzo, Meyerhoff, & Nixon, 2010; Hernan, Alonso, & Logroscino, 2008; Reitz et al., 2005; Richards et al., 2003; Swan & Lessov-Schlaggar, 2007), hypertension (Brady et al., 2005; Harrington et al., 2000; Kivipelto, Helkala, Laakso, Hanninen, Hallikainen, Alhainen, et al., 2002; Launer, Ross, Petrovitch, Masaki, Foley, White, Havlik, 2000; Reitz, Tang, Manly, Mayeux, & Luchsinger, 2007; Singhmanoux & Marmot, 2005; Skoog, Lernfelt, Landahl, Palmertz, Andreasson, Nilsson, et al., 1996; Whitmer, Sidney, Selby, Johnston, Yaffe, 2005; Wu, Zhou, Wen, Zhang, Como, Qiao, 2003), and diabetes mellitus (Allen, Frier, & Strachan, 2004; Awad, Gagnon, & Messier, 2004; Biessels, Staekenborg, Brunner, Brayne, & Scheltens, 2006; Christman, Vannorsdall, Pearlson, Hill-Briggs, & Schretlen, 2010; Ott, Stolk, van Harskamp, Pols, Hofman, Breteler, 1999; Whitmer, 2007).

Although vascular risk is frequently discussed in the context of processing speed and executive functioning impairments (Schmidt, Ropele, Enzinger, Petrovic, Smith, Schmidt, et al., 2005; van den Heuvel, ten, de Craen, dmiraal-Behloul, Olofsen, Bollen, et al., 2006), cognitive functioning in other domains, including episodic memory, is also commonly impacted among those with elevated vascular burden (Bangen et al., 2009; 2010; Brady et al., 2005; Edelstein et al., 1998; Elias, Elias, Sullivan, Wolf, & D'Agostino, 2005; Harrington et al., 2000; Hill et al., 2003; Kalmijn et al., 2002; Luchsinger et al., 2005; Paul et al., 2006; Reitz et al., 2005; Richards et al., 2003; Sabia et al., 2008; Schinka et al., 2003; Singh-Manoux & Marmot, 2005; Starr et al., 2006; Stewart et al., 2006; Zade et al., 2010). For instance, Bangen and colleagues (2010)

examined the relationship of stroke risk (including vascular risk and disease), depression, and genetic factors with cognition in cognitively normal older adults as well as adults with Alzheimer's disease. They found that, across the entire sample, greater stroke risk was associated with impairments in episodic memory and processing speed. Indeed, episodic memory was the cognitive domain most strongly impacted by vascular factors, although these relationships disappeared when each diagnostic group was considered separately, perhaps due to insufficient power (Bangen et al., 2010). Nevertheless, this work suggests that vascular risk and disease have a significant impact on episodic memory performance. Llewellyn and colleagues (2008) also examined the impact of stroke risk on cognition in a large, prospective, population-based study. They found that after controlling for age, sex, and confounds of cognitive functioning, increased stroke risk predicted significantly lower levels of global cognition, immediate and delayed verbal memory, semantic fluency, and processing speed. Goldstein et al. (2008) similarly demonstrated a deleterious effect of an index of vascular risk (i.e., hypertension and hypercholesterolemia) on verbal and visual recall among patients with mild to moderate Alzheimer's disease (AD) compared to AD patients without vascular risk factors. Consequently, it is clear that composite indices of vascular risk are strong predictors of cognitive decline in old age, particularly in episodic memory.

Research examining individual vascular risk factors has also reported associations with episodic memory in older adults. Hypertension has frequently been associated with increased risk for cognitive decline in old age, although it appears that mid-life hypertension carries a higher risk for cognitive decline than hypertension with onset in

older adulthood (Elias, Wolf, D'Agostino, Cobb, & White, 1993; Hughes & Ganguli, 2009; Jennings & Zanzstra, 2009; Tzourio, 2007; Zade et al., 2010). Zade and colleagues (2010) investigated the effect of cumulative stroke risk as well as individual vascular risk factors on cognition in a large community based longitudinal study. They found that cumulative stroke risk interacted with genetic vascular risk (i.e., carrier of the apolipoprotein E ϵ 4 allele) to predict decrements in verbal and non-verbal memory and executive functions. Importantly, this effect was driven in part by systolic blood pressure, which was the only individual risk factor to show significant relations with cognition. Also studying systolic blood pressure in a lifespan sample of adults aged 17 to 77, Bender and Raz (2012) found that systolic blood pressure partially accounted for the impact of age on episodic memory performance, such that older individuals had increasing systolic blood pressure and poorer memory recognition performance. In a subset of the sample at genetic risk for vascular disease, the effects of increasing systolic blood pressure on recognition memory performance were further mediated by lateral prefrontal volumes but not hippocampal volumes, suggesting blood pressure may exert its influence on memory performance beyond the medial temporal lobes (Bender & Raz, 2012). Indeed, memory impairment associated with vascular risk is often conceptualized in terms of disruption in frontally-mediated retrieval from memory stores, use of learning and memory strategies, and ability to distinguish relevant from irrelevant information in memory stores (Sachdev, Brodaty, Valenzuela, Lorentz, Looi, Wen, & Zagami, 2005). Such frontally-mediated memory impairments produce a clinical presentation distinct from that seen in Alzheimer's disease, which is instead characterized by an inability to encode and store

information in long-term memory, functions subserved by the medial temporal lobes (Mesulam, 2000).

Similar declines in episodic memory have been noted among individuals with type 2 diabetes (Grodstein, Chen, Wilson, & Manson, 2001; McFall, Geall, Fischer, Dolcos, & Dixon, 2010; Messier, 2005; Umegaki, Kawamura, Kawano, Umemura, Kanai, & Sano, 2011; Verdelho, Madureira, Moleiro, Ferro, Santos, Erkinjuntti, et al., 2000). In fact, one comprehensive review of the literature suggested that verbal episodic memory and processing speed are the most commonly impaired cognitive domains in type 2 diabetes (Awad et al., 2004). Yet others have noted that memory impairments are not as robust in younger type 2 diabetics, suggesting that type 2 diabetes may synergistically interact with age-related cognitive decline to produce prominent memory dysfunction primarily in older type 2 diabetics (Ryan & Geckle, 2000). Bruehl and colleagues (2009) demonstrated impairments in immediate and delayed verbal episodic memory among individuals with type 2 diabetes compared with healthy controls. A cross-sectional study of elderly adults with and without type 2 diabetes also revealed the deleterious impact of diabetes on immediate and delayed memory performance (Yau, Javier, Tsui, Sweat, Bruehl, Borod, & Convit, 2009). Furthermore, immediate memory performance was associated with reduced white matter integrity in the temporal lobes, suggesting that diabetes may exert at least some of its effects on memory through white matter damage (Yau et al., 2009). Two large epidemiological studies of diabetes mellitus in middle-aged adults also found diabetics to have a higher risk of memory impairment and a steeper decline in verbal learning and memory over a six year interval, differences

which were maintained after controlling for other cardiovascular risk factors (Knopman, Bolland, Mosely, et al., 2001; Luchsinger, Reitz, Patel, et al., 2007). Importantly, level of glycemic control in diabetics appears to modulate the degree of cognitive dysfunction observed, with poorer control leading to worse cognitive outcomes (Kodl & Seaquist, 2008; Kumar, Looi, & Raphael, 2009). In fact, impaired glucose tolerance has also been associated with reduced long-term memory abilities even in patients without diabetes (Vanhanen, Koivisto, Kuusisto, Mykkanen, Helkala, Hanninen et al., 1998). Moreover, hypoglycemia which can result from attempts to control hyperglycemia through intense insulin management can also produce impairments in learning and memory (Hughes & Ganguli, 2009; Kodl et al., 2008; Sommerfield, Deary, McAulay, & Frier, 2003; Warren, Zammitt, Deary, & Frier, 2007; Widom & Simonson, 1990), although this finding is not consistent in the literature and may depend on the age of the patients examined and age of onset of diabetes (Hughes & Ganguli, 2009; Kodl et al., 2008). Thus, there exists a complex interplay of factors that can produce cognitive impairment in patients with diabetes (Hughes & Ganguli, 2009; Kodl et al., 2008; Kumar et al., 2009).

Cigarette smoking has also been found to be associated with cognitive decline in prospective studies, although this finding appears most robust in current instead of former smokers, and conflicting findings regarding the effect of smoking on cognition exist in the literature (Anstey et al., 2007; Collins et al., 2009; Reitz et al., 2005; Richards et al., 2003). One study by Reitz and colleagues investigated cognitive functioning in elderly current, former, and never smokers across a 5-year period. Interestingly, they found that only current smokers showed evidence of increased cognitive decline, and only when

they were over the age of 75. These individuals demonstrated a more rapid decline in memory performance compared to former or never smokers of the same age (Reitz et al., 2005). Similar findings were reported in a study by Richards et al. (2003), which indicated that smoking during midlife predicted a more rapid decline in verbal memory ten years later, although this association was strongest for those who smoked more than 20 cigarettes a day. In a study focusing on the effects of cigarette smoking among older adults of Mexican descent, Collins et al. (2009) found a steeper rate of cognitive decline as measured by the Mini Mental State Exam (MMSE) for smokers than non-smokers. Although the authors did not report whether decline varied by cognitive domain, it is nonetheless striking that cigarette smokers showed greater decline on a cognitive screening measure known to be insensitive to subtle changes in cognition. Anstey and colleagues (2007) performed a meta-analysis of studies examining the relationship of smoking history with incidence of dementia in older adults, including Alzheimer's disease and vascular dementia. The authors found that current smokers had an increased risk of developing Alzheimer's disease and a steeper decline in global cognitive functioning (as measured by the MMSE) compared to both former smokers and never-smokers. Former smokers did not show an increased incidence of dementia compared to never-smokers, although they did display increased rate of decline in global cognition, demonstrating the lingering effects of smoking even after a period of abstinence (Anstey et al., 2007). Thus, smoking appears to have an impact on cognition in general and episodic memory in particular, although its effects may be most pronounced among current smokers.

Yet it should be noted that not all studies examining vascular risk have reported deleterious effects on episodic memory. For instance, Christman et al. (2010) examined neuropsychological performance in diabetic and non-diabetic middle aged and older adults. While diabetics demonstrated impairments in working memory, processing speed, and fluency relative to their non-diabetic counterparts, there were no group differences in verbal or visual episodic memory. However, this study had a relatively small sample of diabetic participants and thus may have been underpowered to detect subtle changes in some cognitive domains (Christman et al., 2010). Gunstad and colleagues (2009) examined the impact of hypertension and blood pressure variability on cognition in older adults with cardiovascular disease (including heart attack, cardiac surgery, heart failure, coronary artery disease, and hypertension). They found that blood pressure variability actually exhibited a positive relationship with episodic memory and language, a finding contradicting much of the literature in this area. The authors suggest that perhaps hypertension produces different sequelae in adults with cardiovascular disease versus otherwise healthy adults. Alternatively, it is possible that hypertension has minimal effects in well-managed cardiovascular disease, with other factors such as hypoperfusion accounting for much of the cognitive decline observed in this population. Indeed, all the participants in this study were followed by a cardiologist and as a result had well-managed hypertension, whereas poorly managed hypertension has been most associated with cognitive decline in the literature (Gunstad, Keary, Poppas, Paul, Jefferson, Sweet et al., 2009). Two additional studies examining cumulative stroke risk also failed to find a relation between stroke risk and verbal episodic memory (Brady, Spiro, McGlinchey-

Berroth, Milberg, & Gaziano, 2001; Elias et al., 2004), although one of them reported a negative relationship between stroke risk and visual memory (Elias et al., 2004).

However, both of these studies had methodological limitations including unrepresentative samples and failure to control for confounding factors in analyses.

Current Study

Description and purpose. Advancing age in non-demented older adults is commonly associated with subtle cognitive declines, particularly in episodic memory. Recent developments in the field of cognitive neuroscience have piqued researchers' interest in alterations in functional connectivity within higher-order neural networks as an explanation for age-related cognitive decline. This line of research has demonstrated decrements in the functional connectivity of the so-called default-mode network (DMN) in old age. The DMN is a network of spatially distributed brain regions whose neural activity are closely temporally related, and is thought to underlie self-relevant, task-independent thought reliant on episodic memory. Disruptions in DMN connectivity are also associated with cognitive decline in several domains, most notably episodic memory.

Despite the consistency in these findings, the etiology of age-related disruptions in DMN functional connectivity remains elusive. A compelling possibility that to this point has been surprisingly unexplored is the role of vascular risk factors, such as hypertension, diabetes, and cigarette smoking, in producing functional connectivity disruptions. Vascular risk factors are highly common with increasing age and are well-known to induce both gray matter atrophy and white matter degeneration with subsequent declines in episodic memory. Importantly, functional connectivity of neural networks

depends on the integrity of the brain regions composing the network. If a network region experiences disproportionate cell death as occurs in gray matter atrophy or disconnection from other brain regions through white matter damage, the efficiency of network communication, and thus network functional connectivity, will be attenuated.

Consequently, it is plausible that vascular risk, so common with advancing age, could be a primary instigator for the functional connectivity disruption and associated episodic memory decline observed in older adults. Were this indeed the case, health initiatives targeting vascular risk factors among older adults could not only reduce the incidence of dementia associated with vascular burden, saving millions of dollars in health costs annually, but could also slow or halt the cognitive declines observed in relatively healthy older adults.

Despite the obvious importance of understanding the impact of modifiable vascular risk factors on cognitive outcomes in advancing age, no study has yet investigated the impact of vascular risk on functional connectivity and episodic memory in non-demented older adults. The current study sought to do just this using archival data from a large community-based sample of non-demented older adults who received a neuropsychological assessment and resting-state functional magnetic resonance imaging. Functional connectivity values of the posterior cingulate cortex (PCC), the primary node of the DMN, were gathered using seed-based voxel-wise analysis. Vascular risk was assessed through a composite variable denoting the presence of three major vascular risk factors, hypertension, diabetes, and cigarette smoking. Episodic memory was measured through a composite of seven well-normed neuropsychological assessments.

Whether vascular risk and episodic memory were associated with functional connectivity of the PCC to other regions throughout the brain was investigated with separate correlation maps corrected for multiple comparisons. Functional connectivity values of the PCC with other well-established nodes in the DMN, namely ventromedial prefrontal cortex, hippocampus, and inferior parietal lobe, were then extracted. These values were used as indicators for a latent variable representing the DMN using confirmatory factor analysis. As will be discussed in the Results, the FC values did not form a coherent latent variable. Thus, the FC between the PCC and the ventromedial prefrontal cortex, the other major DMN hub, was used as a proxy for DMN FC in a path analysis with PCC functional connectivity mediating the relationship between vascular risk and episodic memory. Finally, as an additional test of the proposed mediational model, it was compared to an alternative model in which depressive symptomatology acted as the mediator between vascular risk and episodic memory in lieu of DMN functional connectivity. This alternative model was selected based on much empirical evidence linking a significant vascular history with the development of late-life depression (e.g., Flicker et al., 2010; Hakim, 2011; Lezak et al., 2004; Sneed & Culang-Reinlieb, 2011). Interestingly, the development of depression among individuals with a high vascular load appears to have neurobiological, as opposed to psychosocial, underpinnings (e.g., Hakim, 2011; Mueller, Mack, Mungas, Kramer, Cardenas-Nicolson, Lavretsky, Greene, et al., 2010; Sneed & Culang-Reinlieb, 2011; Steffens, Taylor, Denny, Bergman, & Wang, 2011). In other words, the degree of association between vascular history and depression cannot be explained by quality of life or other changes

produced by the vascular variable. Instead, there appears to be a complex interplay of vascular, neurobiological, and neurochemical changes that result in close associations between vascular and depressive history. Depression has also often been found to impair episodic memory performance (Bennett et al., 2004; Hakim, 2011; Lezak et al., 2004; Sneed & Culang-Reinlieb, 2011), further substantiating the viability of this alternative model. In the present study, depressive symptoms were measured by a structured questionnaire.

This study sought to make a valuable contribution to the field as the first endeavor to jointly consider vascular risk, PCC functional connectivity, and episodic memory among non-demented older adults. As the prevalence of vascular risk continues to increase in association with the aging of the population, it is vital to fully appreciate their impact on neural integrity and cognition, as well as to determine means of offsetting their deleterious effects. Insights gained by this research may thus provide the field with additional avenues toward enhancing cognition and reducing the incidence of dementia among older adults. Furthermore, because vascular risk was measured retrospectively as the individual's lifetime incidence of several vascular risk factors, this study's design can be thought of as quasi-longitudinal (Cole & Maxwell, 2003). Although this design still has many shortcomings typical of cross-sectional designs, it nevertheless allows stronger conclusions to be drawn regarding the relationships under investigation, and also paves the way for larger epidemiological studies in this area.

Hypotheses. This study examined the relationship of vascular risk, posterior cingulate cortex (PCC) functional connectivity, and episodic memory performance among community-dwelling non-demented older adults. It was predicted that:

Hypothesis 1: Seeding the PCC would reveal functionally associated regions consistent with the default mode network (DMN).

Hypothesis 2: Functional connectivity of the PCC with other brain regions would positively correlate with episodic memory while covarying age, education, gender, and total gray matter volume.

Hypothesis 3: Functional connectivity of the PCC with other brain regions would negatively correlate with vascular risk while covarying age, education, gender, and total gray matter volume.

Hypothesis 4: When used as latent indicators in a confirmatory factor analysis, the functional connectivity of the PCC with ventromedial prefrontal cortex, hippocampus, and inferior parietal lobe would positively load on a single latent variable representing DMN connectivity while covarying for age, education, and gender and will fit the data significantly better than the null model. A graphical representation of this model is shown below.

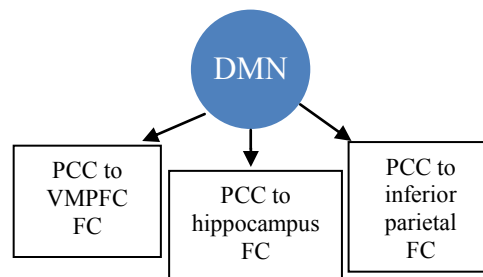


Figure 4. DMN latent variable predicted in Hypothesis 4, with functional connectivity of the PCC with VMPFC, hippocampus, and inferior parietal lobe as indicators.

Hypothesis 5: Vascular risk would negatively predict episodic memory in a structural equation model (M1) while covarying for age, education, and gender and this model would fit the data significantly better than the null model. A graphical representation of this model is shown below.



Figure 5. Structural equation model M1 of vascular risk predicting episodic memory as predicted in Hypothesis 5.

Hypothesis 6: In a structural equation model (M2), vascular risk would negatively predict DMN connectivity and episodic memory, while DMN connectivity would positively predict episodic memory while covarying for age, education, and gender, and this model would provide a significantly better fit to the data than the null model and the model described in Hypothesis 5. A graphical representation of this model is shown below.

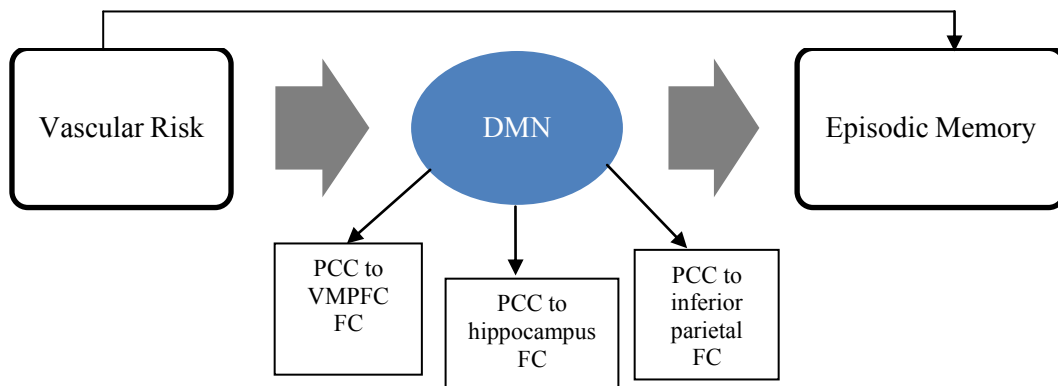


Figure 6. Structural equation model M2 allowing vascular risk to predict the DMN latent variable and episodic memory and allowing the DMN latent variable to predict episodic memory as predicted in Hypothesis 6.

Hypothesis 7: The effect of vascular risk on episodic memory would be significantly reduced when adding the DMN latent variable to the model, so that DMN functional connectivity partially mediated the relationship between vascular risk and episodic memory.

Hypothesis 8: The addition of depressive symptomatology to the model described in Hypothesis 6 as an alternative mediator between vascular risk and episodic memory (M3) would not significantly improve model fit. Moreover, the removal of DMN functional connectivity from the full model containing depressive symptomatology (M4) would significantly reduce model fit. The alternative model (M3) is shown below in Figure 7.

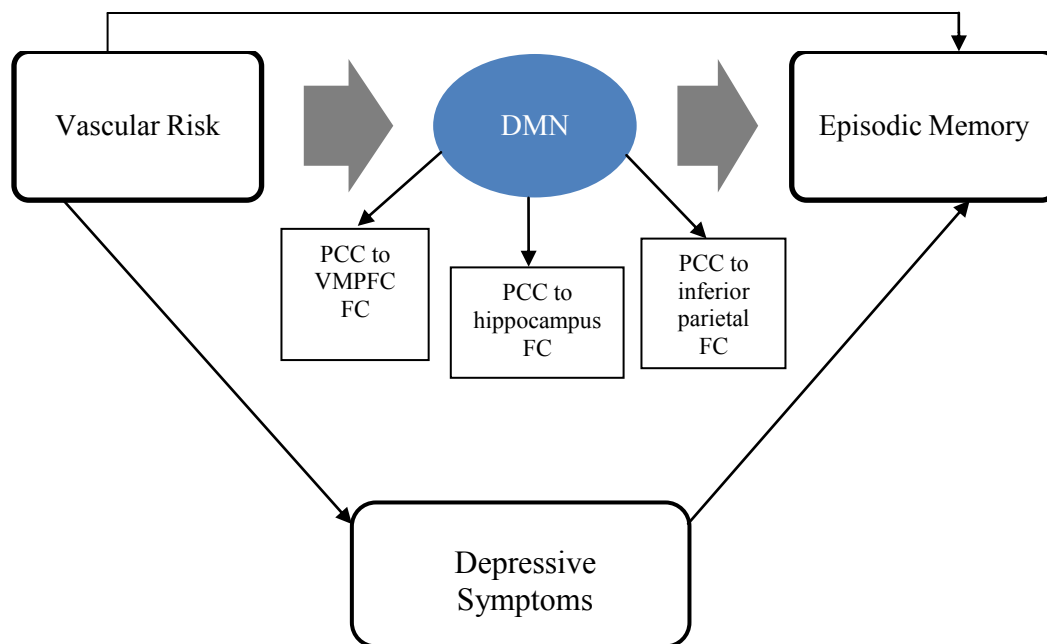


Figure 7. Alternative structural equation model (M3) described in Hypothesis 8, including depressive symptoms as a mediator between vascular risk and episodic memory. M4 would retain all paths except those to and from the DMN latent variable.

CHAPTER THREE

METHODS

Participants

Data from 152 non-demented older adults was drawn from a community sample of older adults recruited for a longitudinal clinical-pathological study of aging.

Demographic information for the sample is provided in Table 1. The sample was composed of 75% women ($n = 114$) and 25% men ($n = 38$), 98% of whom ($n = 149$) were Caucasian. The sample had an average age of 81.45 years ($SD = 7.11$) and an average educational level of 15.53 years ($SD = 3.07$). Overall, participants had an average of 1.18 vascular risk factors ($SD = 0.81$). Within that, 21.7% of the sample ($n = 33$) had no vascular risks, while 57.9% of participants ($n = 88$) had a history of hypertension, 9.9% ($n = 15$) had a history of Type I diabetes, and 46.7% ($n = 71$) had a history of cigarette smoking.

Table 1. Sample Demographic Information

	Age	Gender	Race	Education	Vascular Risk
Mean	81.45	75% female	98% Caucasian	15.53	1.18
Standard Deviation	7.11	--	--	3.07	0.81

The participants were selected for inclusion in the current study based on having received a resting-state fMRI scan, neuropsychological testing demonstrating the absence

of dementia, depressive symptomatology questionnaire, and information on vascular risk gathered from structured interview, clinical examination, and medication review. In the larger study participants were originally recruited for, the presence of cognitive impairment was determined according to the criteria of the joint working group of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (McKhann, Drachmann, Folstein, Katzman, Price, & Stadlan, 1984) with 11 cognitive assessments frequently used for the diagnosis of dementia. These assessments were administered by a trained technician and scored by a computer, which utilized education-adjusted norms to create impairment profiles for each participant. A board-certified neuropsychologist then examined the cognitive test results, impairment ratings, as well as information on education, occupation, sensory or motor deficits, and effort, to come to a decision regarding the presence of cognitive impairment for each participant. A physician with expertise in the diagnosis of dementia then evaluated each participant to assess for the presence of deficits in daily functioning and a significant decline in cognitive ability from previous levels. Participants were diagnosed with dementia if they exhibited significant cognitive impairment in memory and at least one other cognitive domain and were also impaired in functional activities of daily living. Participants were diagnosed with mild cognitive impairment if they had cognitive impairment but did not meet full criteria for dementia. Participants deemed to be free of dementia and mild cognitive impairment were eligible for inclusion in the present study's sample. All participants gave written informed consent prior to their participation in the larger longitudinal study.

Demographic, Health, and Mood Variables

Participant demographics were collected after the individual gave consent to participate in the larger study. Demographics included the participant's age, education, gender, and ethnicity. Information on vascular risk, namely hypertension, diabetes, and cigarette smoking, was gathered from structured interview, clinical examination, and medication review. Participants were recorded as having a specific vascular risk factor if they experienced it at any point in their lives, not necessarily at the time of data collection. The three vascular risk factors were combined to form a composite vascular risk variable ranging from 0 (no risk factors) to 3 (all three risk factors).

Depressive symptomatology was measured with the Center of Epidemiological Study-Depression scale (CES-D; Radloff, 1977). The CES-D is a self-report measure consisting of 10 items designed to detect depression among individuals in the general population. Each person's score is the number of depressive symptoms (i.e., items) they endorsed out of 10. The current study used participants' average CES-D scores across the span of time they participated in the larger longitudinal study they were originally recruited for.

Neuropsychological Assessment

All participants were given a comprehensive neuropsychological evaluation after recruitment for the larger, longitudinal study from which this study's participants were drawn. This study focused only on those neuropsychological tests assessing episodic memory. Seven tests were used to measure episodic memory, including Word List Memory, Word List Recall, and Word List Recognition from the Consortium to Establish

a Registry for Alzheimer's Disease (CERAD) procedures (Morris, Heyman, Mohs, et al., 1989), immediate and delayed recall of Logical Memory Story A (Wechsler, 1987), and the East Boston Story (Albert, Smith, Scherr, et al., 1991). Each participant's scores on the seven memory assessments were transformed into z-scores and averaged to create a composite measure of episodic memory by a statistician.

Word List Memory. The Word List Memory test was included in the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery (Morris et al., 1989). For the test, participants are asked to read aloud printed cards listing 10 items to remember. Immediately after reading the items, the participant is asked to recall as many as possible. This procedure is repeated for two additional trials, with a different order of item presentation each time. Participants are asked to recall the 10 previously studied items 15 minutes later, and are then asked to recognize the previously studied words which are presented along with 10 new words.

WMS-R Logical Memory subtest. The Wechsler Memory Scale – Revised (WMS-R) consists of subtests designed to assess different aspects of a person's memory (Wechsler, 1987). The Logical Memory subtest requires participants to listen to a short story, after which they are to recall as much of the story as they can, as close to the original words as possible. A second short story is read and recalled in a similar fashion. This second story is read a second time, and the participant is asked to attempt to recall the story again. After a 25 minute delay, the participant is again asked to recall both the

first and second story. Participants' scores are determined by the number of individual items they recall from each story.

East Boston Story. The East Boston Story (Albert et al., 1991) consists of a short story that is read to the participant, who then is asked to repeat the story back using as close to the original wording as possible. The participant is then asked to recall the same story again after a 20 minute delay.

Resting State fMRI Acquisition and Data Processing

Participants were scanned using a 1.5 Tesla clinical scanner (General Electric, Waukesha, WI) and were not given specific instructions for the rest period. High-resolution T1-weighted anatomical images were collected with a 3D magnetization-prepared rapid acquisition gradient-echo sequence, while resting-state data were acquired using a 2D spiral in/out echo-planar imaging sequence. The images were stripped of all skull material and segmented into gray matter, white matter, and cerebrospinal fluid compartments. Residual non-brain material was manually removed when necessary. Whole-brain volume was determined and used as a covariate in the present study's analyses. The first five volumes from the resting-state scans were discarded so the data would not include images before reaching signal equilibrium. Through Statistical Parametric Mapping software version 8 (SPM8; Friston, Passingham, Hutt, Heather, Sawle, & Frackowiak, 1995), all volumes were corrected for motion, co-registered to the T1-weighted anatomical images, and spatially normalized using the Montreal Neurological Institute (MNI) template. The resulting normalized image volumes were then spatially smoothed with a 4-mm full-width half-maximum Gaussian kernel. A band-

pass filter of 0.01 to 0.08 Hz was then applied to the data to eliminate the effect of cardiac and respiratory variables on the BOLD signal.

Procedure

Prior to participation, participants provided written informed consent for a larger, longitudinal study. Participants then received a neuropsychological battery to assess for cognitive impairment and episodic memory functioning. Only those participants who are free from dementia and mild cognitive impairment were included in the present study. Eligible participants also underwent resting-state functional magnetic resonance imaging and received a questionnaire, structured interview, and clinical evaluation to assess for depression and vascular risk factors.

Data Analysis

Functional connectivity analysis. Functional connectivity analyses were conducted with the Resting-State fMRI Data Analysis Toolkit (REST: <http://restfmri.net/forum/REST>) using a voxel-wise seed-based region of interest (ROI) approach. In light of the research suggesting that the posterior cingulate cortex (PCC) is the major hub of the default mode network (DMN) and functional connectivity maps based on the PCC provide the closest fit to the DMN, the PCC was used as a seed region. A spherical seed ROI with a 4mm radius was prescribed in the PCC with MNI coordinates of $x = 0$, $y = -53$, $z = 26$, in accordance with previous research (Hedden et al., 2009). A mean signal time course was created for the seed and used as a reference in the functional connectivity analysis. Cross-correlations were conducted between the reference signal time course and the time series in each other voxel throughout the brain

while controlling for age, education, gender, and total gray matter volume. Voxels with a minimum cluster size of five whose activity significantly correlate with the activity of the PCC seed region were identified with an alpha-value corrected for multiple comparisons ($\alpha = 0.0001$) according to a whole-brain Fisher's z-transformation of each individual correlation value. The above analytic steps were used to assess Hypothesis 1. The resulting Fisher's z-transformed functional connectivity values were then extracted and used in two separate partial correlation analyses with vascular risk and episodic memory to determine their relationship with PCC functional connectivity in each voxel of the brain while controlling for age, education, gender, and total gray matter volume. These steps assessed Hypotheses 2 and 3. An alpha-value of 0.001 was used in partial correlation analyses to control for multiple comparisons. Finally, Fisher's z-transformed values were extracted for the functional connectivity of the PCC and the VMPFC, hippocampus, and inferior parietal lobe to be used in structural equation modeling analyses.

Age, education, gender, and total gray matter volume were selected as covariates in the above analyses in accord with accepted practice in the field. Age is often used as a covariate with neuroimaging data because it is correlated with several relevant neuroimaging characteristics, including overall and region-specific brain volume, as well as with cognition (Lezak et al., 2004). Gender is often similarly controlled for because of sex-specific differences in brain size and structure (e.g., Kolb & Whishaw, 2009; Lezak et al., 2004). Education is often controlled for because of its associations with brain function, cognition, and its role as a protective factor against neurodegeneration in old

age (i.e., cognitive reserve, Lezak et al., 2004; Stern, 2009). Finally, total gray matter volume is also controlled for in functional imaging analyses to address partial volume effects, in which an individual's total gray matter volume and ratio of gray to white brain matter can impact indices of brain function (e.g., Bokde, Pietrini, Ibanez, Furey, Alexander, Graff-Radford, et al., 2001; Liang et al., 2011).

Structural equation modeling analyses. Structural equation modeling analyses proceeded in a series of three steps. First, two linear regression analyses were conducted with education, age, and gender predicting episodic memory and depressive symptomatology. Unstandardized residuals of episodic memory and depressive symptomatology were saved from these regressions to use in structural equation modeling. This allowed the structural equation models to control endogenous variables for education, age, and gender as covariates. These covariates were chosen following the same rationale discussed above for covariate selection in the functional connectivity analyses. Ethnicity was not used as a covariate because although race may impact an individual's level of vascular risk, there is no empirical work to suggest it would impact the nature of the relationships among vascular risk, PCC functional connectivity, and episodic memory. Prior to conducting the structural equation modeling analyses, the data was also assessed for multivariate normality in PRELIS (Jöreskog & Sörbom, 2006) using Mardia (1970) tests of skewness and kurtosis.

In the subsequent steps of analyses, structural equation modeling was conducted using LISREL 8.8 (Jöreskog & Sörbom, 2006), analyzing covariance matrices via maximum likelihood (ML) estimation. Regarding power to detect significant effects in

the structural equation models, the established standard in the field is to have a minimum of five to ten participants per estimated parameter in the model (Bentler, 1995). The maximum number of parameters estimated in the proposed structural equation models in the current study was 12, with approximately 13 participants per parameter in a sample with 152 participants. Thus, the present study exceeds the minimum standard for sufficient power to detect significant effects. Using the empirically-based procedure to determine power to detect mediation recommended by Fritz and MacKinnon (2007) and assuming partial mediation and medium direct effect sizes among the study variables, the current sample of 152 was estimated to provide sufficient power (i.e., .80) to detect at least a moderate mediation effect when using the Baron and Kenny approach to detect mediation. In addition, the current sample was estimated to provide sufficient power to detect at least a small mediation effect when using bias-corrected bootstrapping to detect mediation.

The degree of model fit to the data was assessed using measures of absolute and relative fit. Measures of absolute fit include the root mean square error of approximation (RMSEA), which gauges model misfit, in that a zero value for this index represents perfect fit, while larger values represent poorer fit. RMSEA values greater than 0.10 represent unacceptable fit, values between .08 and .05 represent relatively close fit, and values less than .05 represent good fit (Browne & Cudeck, 1993). Standardized root mean residual (SRMR) was also used as a measure of absolute fit, representing the size of residuals among the observed and predicted covariances. Thus, smaller values of SRMR are preferable, with a value of less than 0.08 denoting acceptable model fit (Hu &

Bentler, 1998). Two measures of relative fit were also used. These included the comparative fit index (CFI), representing the improvement in fit of the tested model over the null model, which hypothesizes no covariances among variables. Therefore, larger values of CFI are desirable, with a common cut-off being greater than 0.90. This is similar to the second indicator of relative fit, the normed fit index (NFI), which also uses a cut-off value of greater than 0.90. Finally, preliminary analysis suggested the data were nonnormal; thus, Satorra-Bentler's scaled chi-square for robust maximum likelihood estimation was also used to assess model fit. Chi-square difference testing of scaled Maximum Likelihood (ML) Satorra-Bentler chi-square values were conducted according to the recommendations of Bryant & Satorra (2012). In examining path coefficients within each model, Type 1 error rate was controlled using Benjamini-Hochberg's (1995) false discovery rate controlling step-up Bonferroni procedure. This procedure was found in a Monte Carlo study to have the best balance between controlling the Type 1 error rate while preserving power to detect significant effects (Cribbie, 2007).

In the second step of structural equation analyses to assess Hypothesis 4, a confirmatory factor analysis (CFA) was conducted using the functional connectivity values of the PCC with the VMPFC, hippocampus, and inferior parietal lobe (IPL) as measured indicators for a latent DMN variable. The factor loadings of the right and left hippocampus and right and left inferior parietal lobe indicators were constrained to be equal in the CFA model, while the VMPFC loading was fully free to estimate. This was done in light of research suggesting that the VMPFC hub is highly functionally connected with the PCC, while the hippocampus and inferior parietal lobe are connected to the PCC

to a relatively lesser degree (Andrews-Hanna et al., 2010). Relative and absolute fit indices were examined as described above to determine whether the CFA model fits the data significantly better than the null model, which hypothesizes no significant connections among indicators. The individual loading of each functional connectivity indicator was also examined to determine whether the indicator was significantly associated with the resultant latent variable. As will be discussed in the Results section, the indicators did not form a coherent latent variable in the CFA model. Therefore, the functional connectivity value of the PCC with the VMPFC was instead used in subsequent models as a proxy for the DMN. The PCC-VMPFC functional connectivity was chosen based on research suggesting these are the two main hubs for the posterior and anterior subnetworks of the DMN, respectively (Andrews-Hanna et al., 2010; Stawarczyk et al., 2011; Uddin et al., 2009).

Then, as part of the third step of structural equation analyses, path analyses were conducted according to the recommendations of Baron and Kenny (1986) to evaluate VMPFC FC as a mediator of the relationship between vascular risk and episodic memory. To assess Hypothesis 5, a path analysis was conducted in which vascular risk was allowed to predict episodic memory (M1). The fit of this model compared to the null model was assessed by examining absolute and relative fit indices as described above, and the individual path coefficient for the prediction of episodic memory by vascular risk was also evaluated. Next, to assess Hypothesis 6, vascular risk was allowed to predict the VMPFC functional connectivity variable and episodic memory, and the functional connectivity variable was also allowed to predict episodic memory (M2). By examining

absolute and relative fit statistics, the fit of this model was compared to that of null model. Using scaled ML chi-square difference tests (Bryant & Satorra, 2012), the fit of this model was also compared to the model assessing Hypothesis 5 (M1) to determine whether the addition of the functional connectivity variable explained a significant amount of covariance above and beyond that explained by the relation of vascular risk with episodic memory. The path coefficients for the effect of vascular risk on the functional connectivity variable and episodic memory, and for the effect of the functional connectivity variable on episodic memory, were also examined to determine the significance and direction of the relationships. To further assess the role of DMN functional connectivity as a mediator between vascular risk and episodic memory as described in Hypothesis 7, bias-corrected bootstrapping was conducted when indicated to determine a confidence interval for the size of the indirect effect of vascular risk on episodic memory. Bootstrapping was chosen instead of other available methods for estimating the size of the indirect effect (e.g., the Sobel test) because it is more powerful and provides a better estimate of the size of the indirect effect for studies with smaller sample sizes or nonnormal data (Preacher & Kelley, 2011).

Finally, as a further test of the proposed model with DMN functional connectivity as a mediator, depressive symptomatology was added to the full model containing vascular risk, DMN FC, and episodic memory as described in Hypothesis 8 (M3). In this alternative model, depressive symptoms were predicted by vascular risk, and in turn predicted episodic memory. A scaled ML chi-square difference test (Bryant & Satorra, 2012) was used to determine whether the addition of depressive symptoms accounted for

a significant amount of covariance above and beyond DMN functional connectivity. Path coefficients for the relationships of depressive symptoms with vascular risk and episodic memory were also examined. Lastly, the comparative importance of DMN functional connectivity as a mediator was also evaluated by removing DMN functional connectivity from the alternative model and assessing whether this attenuated model fit through scaled ML chi-square difference testing (M4).

CHAPTER FOUR

RESULTS

Correlations, means, and standard deviations of study variables are provided in Table 2. Participants scored an average of 0.59 standard deviations above the mean on the episodic memory measures ($SD = 0.51$). Participants' average number of endorsed depressive symptoms was 0.98 ($SD = 1.21$, range = 0 to 6). Thus, participants endorsed relatively low numbers of depressive symptoms and also had intact memory performances, as would be expected given that the sample was non-demented.

Functional Connectivity Analyses

Functional connectivity analyses were conducted utilizing a PCC seed region of interest (ROI) to test hypothesis 1, controlling for age, education, gender, and total gray matter volume. An image showing areas with significant functional connections to the PCC is shown below in Figure 8. Colored regions are significant at a voxelwise level of $p < .0001$, with yellows denoting stronger degrees of functional connectivity. This analysis revealed that the PCC was functionally connected (i.e., showed a significant Fisher's z-transformed correlation) with several distributed brain regions, many of which have been linked to the DMN (see Table 3). Specifically, the PCC showed significant functional associations with a large cluster centering in bilateral posterior cingulate cortex, anterior cingulate cortex, medial and lateral parietal, temporal, frontal, and occipital regions, basal ganglia, thalamus, and cerebellum ($t = 99.0541$).

Table 2. Means, Standard Deviations, and Correlations among Study Variables

	1	2	3	4	5	6	7	8	9	10	11	12
1. Vascular Risk	--											
2. Episodic Memory	-.17*	--										
3. Depression	.18*	-.17*	--									
4. VMPFC FC	-.04	-.08	-.14	--								
5. Left HC FC	.01	-.04	.04	.06	--							
6. Right HC FC	-.04	.02	-.01	.03	.50***	--						
7. Left IPL FC	.18*	-.05	.07	.08	-.03	-.11	--					
8. Right IPL FC	.06	-.04	.08	.21**	-.04	.04	.28***	--				
9. Age	-.10	-.02	.07	-.17*	-.27***	-.17*	.02	-.05	--			
10. Education	-.14	.34***	-.24**	.01	-.10	-.16	-.08	-.07	-.01	--		
11. Memory Residual	-.10	.90***	-.11	-.16*	-.04	.02	-.04	-.04	.00	.00	--	
12. Depression Residual	.17*	-.10	.97***	-.14	.03	-.04	.05	.07	.00	.00	-.12	--
Mean	1.18	0.59	0.98	0.24	0.07	0.06	0.31	0.31	81.45	15.53	1.64 x 10 ⁻¹⁷	1.37 x 10 ⁻¹⁶
Standard Deviation	0.81	0.51	1.21	0.21	0.18	0.18	0.20	0.21	7.11	3.07	0.46	1.17

Note. FC = functional connectivity values between the given region and the posterior cingulate cortex; VMPFC = ventromedial prefrontal cortex; HC = hippocampus; IPL = inferior parietal lobule; Residual variables reflect residual unstandardized variance after controlling for age, education, and gender; * $p < .05$; ** $p < .01$; *** $p < .0001$

Also identified were smaller clusters of significance centering in left ($t = 14.1334$) and right ($t = 12.6708$) middle and inferior temporal gyri, right superior temporal gyrus and temporal pole ($t = 5.3737$), left ($t = 4.9808$; $t = 6.2805$) and right ($t = 5.5458$) inferior frontal regions, right cuneus ($t = 4.3835$), left parahippocampal gyrus and fusiform ($t = 5.9131$), left parahippocampal gyrus and hippocampus ($t = 4.7925$), lobules IX and VIII of the bilateral cerebellum ($t = 11.936$), and left ($t = 8.4051$) and right ($t = 9.2762$) Crus I and II of the cerebellum. As will be discussed in more depth shortly, these results are largely consistent with other descriptions of the DMN with resting-state fMRI in the literature, although they do include regions not typically cited as part of the DMN, such as the basal ganglia, thalamus, and cerebellum.

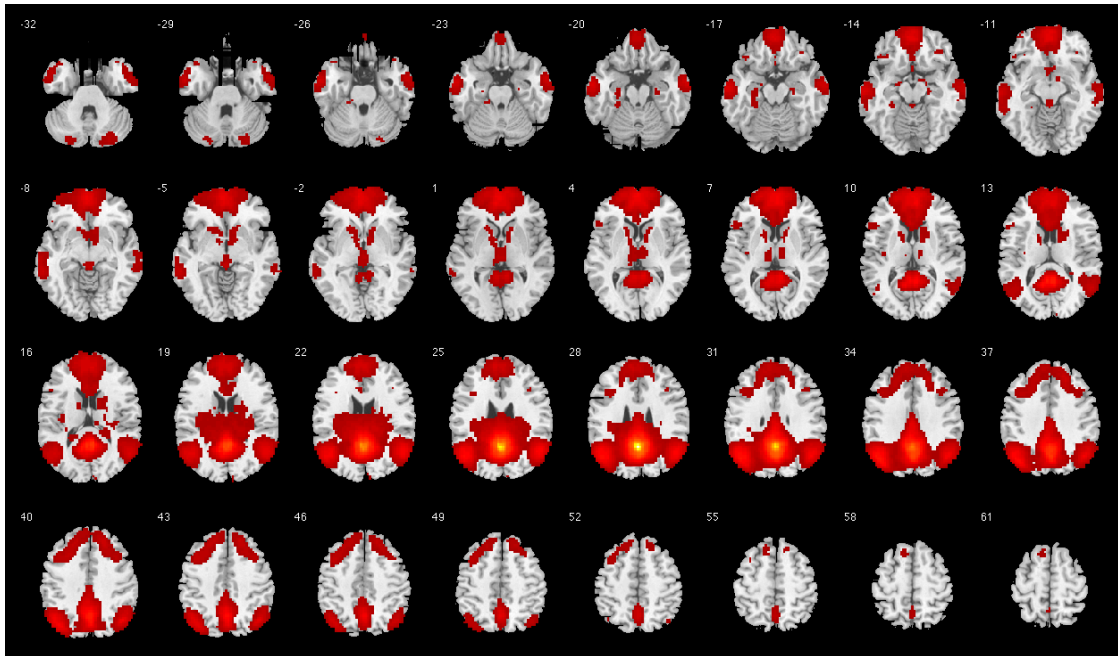


Figure 8. Clusters of significance (voxelwise $p < .0001$) for PCC functional connectivity. Yellows represent stronger degrees of functional connectivity with the PCC.

Table 3. Functional Connectivity Results with Posterior Cingulate Cortex Seed

Region	Cluster Size (# voxels)	Maximum Intensity Voxel Coordinates			<i>t</i> -value
Widespread bilateral posterior cingulate cortex, anterior cingulate cortex, medial and lateral parietal, temporal, frontal, and occipital regions, basal ganglia, thalamus, and cerebellum	11,158	0	-54	27	99.0541
Left middle and inferior temporal gyri	509	-60	-12	-18	14.1334
Right middle and inferior temporal gyri	387	63	-6	-21	12.6708
Lobules IX and VIII of bilateral cerebellum	204	6	-54	-42	11.936
Right Crus I and II of cerebellum	259	30	-75	-36	9.2762
Left Crus I and II of cerebellum	154	-27	-81	-39	8.4051
Left inferior frontal	44	-51	24	6	6.2805
Left parahippocampal gyrus and fusiform	54	-27	-36	-18	5.9131
Right inferior frontal	10	33	33	-15	5.5458
Right superior temporal gyrus and temporal pole	6	36	21	-33	5.3737
Left inferior frontal	16	-39	27	-18	4.9808
Left parahippocampal gyrus and hippocampus	5	-18	-9	-15	4.7925
Right Cuneus	10	9	-96	18	4.3835

Fisher's *z*-transformed PCC FC values were extracted and used in partial correlation analyses with episodic memory scores to assess hypothesis 2, while controlling for age, education, gender, and total gray matter volume (see Table 4). Figure 9 depicts brain regions in which functional connectivity with the PCC significantly correlated with episodic memory. Colored regions are significant voxelwise at $p < .001$; blues denote areas of negative correlation, and reds denote areas of positive correlation.

Several areas showed positive correlations, in which higher degrees of functional connectivity with the PCC were associated with better episodic memory performance. Significant clusters included the right fusiform gyrus ($t = 3.4992$), the right fusiform, cerebellum, and parahippocampal gyrus ($t = 3.7236$), the left fusiform and declive of the left cerebellum ($t = 4.4899$), declive of the right cerebellum ($t = 4.0101$), right middle occipital and temporal gyri ($t = 4.3074$), left putamen and amygdala ($t = 3.4759$), and right putamen ($t = 3.7879$). Certain areas also showed negative correlations (shown in blue), in which higher functional connectivity between these regions and the PCC was associated with *poorer* episodic memory performance. Significant clusters included the right fusiform and inferior temporal gyrus ($t = -3.9183$), the left superior occipital lobe and precuneus ($t = -4.1413$), left Crus I and II of the cerebellum and left inferior occipital gyrus ($t = -4.2434$) and the right Crus II of the cerebellum ($t = -3.8927$).

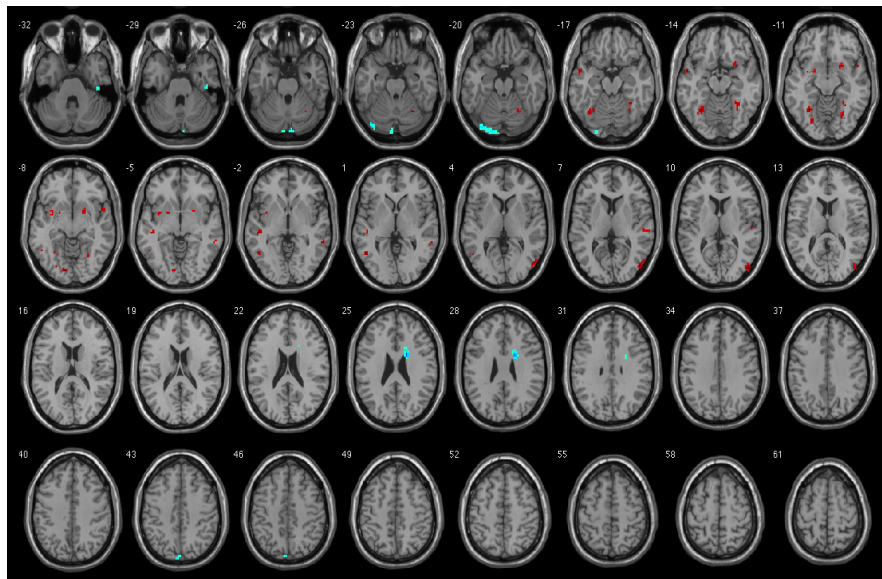


Figure 9. Clusters of significance (voxelwise $p < .001$) showing correlations between PCC FC and episodic memory. Blues denote negative correlations, while reds denote positive correlations.

Table 4. Results of Partial Correlation Analyses with PCC FC and Episodic Memory

Region	Cluster Size (# voxels)	Maximum Intensity Voxel Coordinates			<i>t</i> -value
<u>Positive Correlations</u>					
Left fusiform and declive of cerebellum	24	-30	-57	-12	4.4899
Right middle occipital and middle temporal gyri	27	48	-81	9	4.3074
Right declive of cerebellum	6	27	-60	-24	4.0101
Right putamen	16	21	6	-9	3.7879
Right fusiform, cerebellum, and parahippocampal gyrus	14	30	-48	-15	3.7236
Right fusiform	8	24	-66	-12	3.4992
Left putamen and amygdala	6	-21	3	-6	3.4759
<u>Negative Correlations</u>					
Left Crus I and II of cerebellum and inferior occipital gyrus	44	-36	-84	-21	-4.2434
Left superior occipital lobe and precuneus	6	-3	-84	45	-4.1413
Right fusiform and inferior temporal gyrus	10	45	-27	-33	-3.9183
Right Crus II of cerebellum	5	6	-90	-27	-3.8927

Similar to analyses with episodic memory, partial correlations were also conducted between PCC FC and vascular risk to assess hypothesis 3 (see Table 5). Figure 10 shows areas in which functional connectivity with the PCC significantly ($p < .001$) correlated with vascular risk.

One cluster of subcortical brain regions, including the right caudate and ventrolateral nucleus of the thalamus, showed a significant positive correlation ($t = 3.6496$). Higher levels of vascular risk were associated with *increased* functional connectivity between these regions and the PCC. Two clusters showed significant

negative correlations, indicating that as vascular risk increased, functional connectivity between these areas and the PCC decreased. These included left Crus I, Crus II, and tuber of the cerebellum ($t = -3.4807$) and the left inferior temporal gyrus ($t = -3.5081$).

Table 5. Results of Partial Correlation Analyses with PCC FC and Vascular Risk

Region	Cluster Size (# voxels)	Maximum Intensity Voxel Coordinates			<i>t</i> -value
<u>Positive Correlations</u>					
Right caudate and ventrolateral nucleus of thalamus	10	18	-18	21	3.6496
<u>Negative Correlations</u>					
Left Crus I, Crus II, and tuber of cerebellum	6	-33	-81	-36	-3.4807
Left inferior temporal gyrus	5	-66	-39	-18	-3.5081

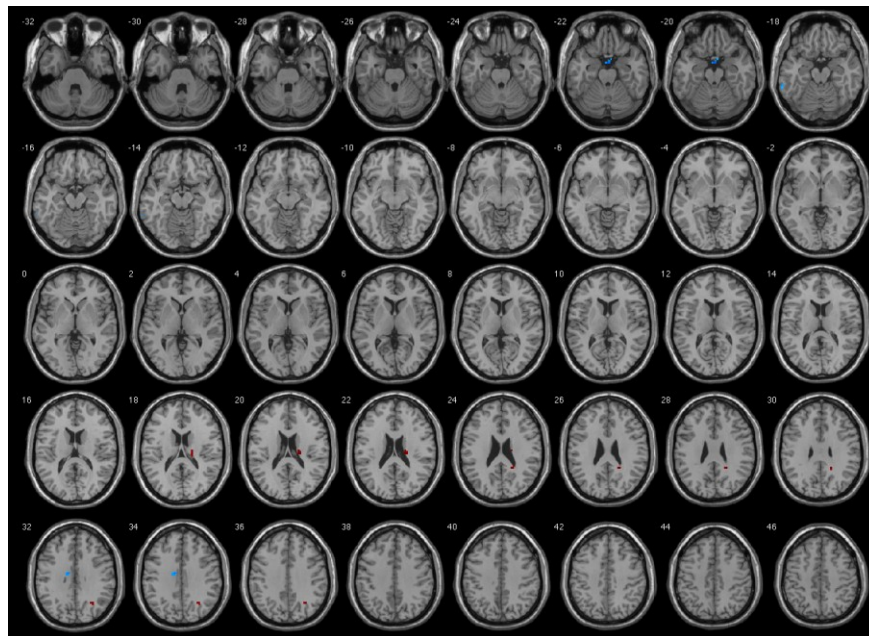


Figure 10. Clusters of significance (voxelwise $p < .001$) showing correlations between PCC FC and vascular risk. Blues denote negative correlations, while reds denote positive correlations.

Structural Equation Modeling Analyses

Prior to structural equation modeling, the data were inspected for significant skewness and kurtosis using Mardia (1970) statistics. Depressive symptoms and vascular risk showed significant univariate skewing and kurtosis, and the data also showed significant departure from multivariate normality. Therefore, maximum-likelihood (ML) estimation was used to compute the Satorra-Bentler scaled chi-square (Bryant & Satorra, 2012; Satorra & Bentler, 1994) to adjust goodness-of-fit statistics for inflation due to nonnormality (Kline, 1998). The Satorra-Bentler scaled ML chi-square was used for both confirmatory factor analysis (CFA) and path analysis. Finally, scaled ML chi-square difference testing was conducted to compare nested path models according to Bryant & Satorra (2012).

Confirmatory factor analysis. CFA was used to fit a model in which FC values between the PCC and ventromedial prefrontal cortex (VMPFC), left and right hippocampus, and left and right inferior parietal lobule (IPL) were used as indicators for a latent variable conceptualized as the DMN. This was done to test hypothesis 4. Equality constraints were used to equate the factor loadings of the left and right hippocampus FC and left and right IPL FC, while the VMPFC FC loading was allowed to be estimated without constraints. This model, along with standardized factor loadings, is shown in Figure 11. Inspection of absolute fit indices revealed that the model provided an overall poor absolute fit to the data, Satorra-Bentler ML scaled χ^2 (8, $n = 152$) = 39.41, $p < .001$, RMSEA = 0.17, SRMR = 0.14. This suggests the model fit significantly worse than a perfect model, which explains all data covariance. Relative fit indices also suggested poor

model fit, CFI = .33, NFI = .31, indicating that this model did not improve fit significantly over the null model, which hypothesizes no linkages among the variables. Indeed, each indicator had significant remaining variance not explained by the model (critical ratios for all theta delta estimates > 6.65 , p 's $< .001$). Moreover, the amount of variance the latent variable explained in each indicator was relatively low, with 14% explained variance in left and right hippocampal FC values, 10% explained variance in left and right IPL FC values, and 6% explained variance in VMPFC FC values. Examination of the factor loadings for each FC indicator shows that bilateral hippocampal and IPL FC indicators loaded significantly on the latent variable (critical ratio for lambda-x estimate = 6.15, $p < .001$), while VMPFC FC was only marginally related to the latent variable (lambda-x critical ratio = 1.72; $p = .085$). Because the proposed latent DMN variable was not supported by the data, VMPFC FC was used in all subsequent path analyses as a proxy for DMN FC. This indicator was chosen apriori based on research suggesting the VMPFC is the major anterior hub of the DMN.

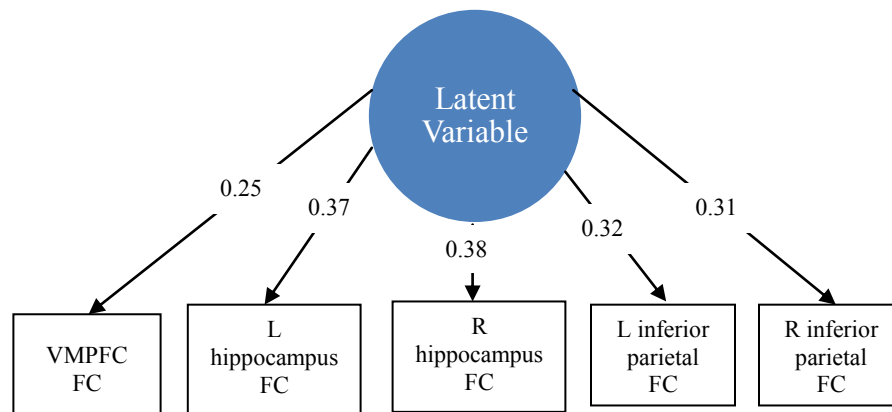


Figure 11. Standardized factor loadings for functional connectivity (FC) values on predicted latent variable. VMPFC = ventromedial prefrontal cortex; L = left hemisphere; R = right hemisphere.

Path analysis. Path analysis was conducted in a series of four nested models to test hypotheses 5 through 8 regarding the ability of DMN FC (operationalized by the functional connectivity between the PCC and VMPFC) and depressive symptoms to mediate the relationship between vascular risk and episodic memory performance. In M1, vascular risk predicted episodic memory. In M2, FC between the VMPFC and PCC was added to M1, so that M2 included vascular risk predicting FC and episodic memory, and FC predicting episodic memory. M3 included depressive symptoms as an additional mediator, so that M3 included all paths in M2, as well as vascular risk predicting depressive symptoms, and depressive symptoms predicting episodic memory. Finally, in M4, VMPFC FC was removed from M3 so that depressive symptoms was the sole mediator of the relationship between vascular risk and episodic memory. Satorra-Bentler scaled ML goodness-of-fit statistics (Bryant & Satorra, 2012) for each model are provided in Table 6.

Table 6. Scaled Goodness-of-Fit Indices for Nested Path Models

Model Tested	Measures of Absolute Fit				Measures of Relative Fit	
	ML Scaled χ^2	Df	RMSEA	SRMR	CFI	NFI
M1	12.63	5	0.10	0.09	0.22	0.20
M2	8.86	3	0.11	0.08	0.37	0.42
M3	1.99	1	0.08	0.04	0.89	0.87
M4	6.92	3	0.09	0.07	0.58	0.55

Note. M1 = Vascular Risk → Episodic Memory; M2 = Vascular Risk → VMPFC FC + Episodic Memory and VMPFC FC → Episodic Memory; M3 = M2 + Vascular Risk → Depressive Symptoms and Depressive Symptoms → Episodic Memory; M4 = Vascular Risk → Depressive Symptoms + Episodic Memory and Depressive Symptoms → Episodic Memory

M1, with vascular risk predicting episodic memory, provided an overall poor fit to the data. All relative fit indices were well outside of the acceptable range, and while one measure of absolute fit fell right at the accepted cut-off (RMSEA = 0.10), the other measure of absolute fit was beyond the accepted cut-off (SRMR = 0.09). Thus, estimating the relationship between vascular risk and episodic memory did not explain a significant amount of variance beyond the null model. M2, including functional connectivity as the mediator of the relationship between vascular risk and episodic memory, provided an overall poor fit to the data. One measure of absolute fit for M2 was outside of the acceptable range (RMSEA = .11), while a second measure of absolute fit fell right at the cut-off for acceptable fit (SRMR = .08). Measures of relative fit for M2 were uniformly poor, indicating that this model did not explain a significant amount of variance beyond the null model. M4, which included only depressive symptoms as a mediator of the relationship between vascular risk and episodic memory, showed acceptable measures of absolute fit, but unacceptable measures of relative fit. Goodness-of-fit statistics indicated that the model with the most acceptable fit was M3, which included both functional connectivity and depressive symptoms as mediators of the relationship between vascular risk and depressive symptoms. M3 had measures of absolute fit that were all in the acceptable range, indicating that the model fit the data nearly as well as a perfect model. However, M3's measures of relative fit were slightly below the accepted cut-off of .90, CFI = .89, NFI = .87, suggesting that model fit could still be improved upon.

Each of these models was directly compared using scaled ML chi-square difference testing (Bryant & Satorra, 2012) to evaluate the relative contribution of FC and

depressive symptoms to model fit. Results of scaled ML chi-square difference testing are given in Table 7. The addition of functional connectivity in M2, in which a path from vascular risk to FC, and a path from FC to episodic memory, were simultaneously added to M1, did not significantly improve model fit, Scaled ML χ^2 Difference Test (2, $n = 152$) = 3.87, $p = 0.14$. This indicates that the relationship of FC with vascular risk and episodic memory did not explain a significant portion of variance in the data beyond the relationship of vascular risk and episodic memory.

In M3, paths from vascular risk to depressive symptoms and from depressive symptoms to episodic memory were added to the relationships in M2, such that both depressive symptoms and FC were included as mediators in the same model. Scaled ML chi-square difference testing revealed that the addition of depressive symptoms to the model significantly improved model fit, Scaled ML χ^2 Difference Test (2, $n = 152$) = 7.20, $p = 0.03$. This suggests that depressive symptoms explain significant variance in the data beyond the relationships among vascular risk, FC, and episodic memory. To further understand the contribution of depressive symptoms to model fit, each path involving depressive symptoms was added sequentially in two separate models (M3_a and M3) to determine whether one or both significantly impacted fit. M3_a, which included all paths in M2 as well as a path from vascular risk to depressive symptoms, significantly improved model fit compared to M2, Scaled ML χ^2 Difference Test (1, $n = 152$) = 5.51, $p = 0.02$. Next, a path from depressive symptoms to episodic memory was added to M3_a in order to create M3, which, as described above, modeled both FC and depressive symptoms as mediators. The addition of a link between depressive symptoms and

episodic memory did not improve model fit, Scaled ML χ^2 Difference Test (1, $n = 152$) = 2.19, $p = 0.14$. Thus, M3, including depressive symptoms as a second potential mediator of the relationship between vascular risk and episodic memory, only improved model fit compared to M2 because of the vascular risk-depressive symptoms link. The link between depressive symptoms and episodic memory did not explain significant variance beyond the relationships modeled in M3_a.

Finally, in M4, paths to and from FC were removed from M3, so that only depressive symptoms remained in the model as the sole mediator. The removal of FC did not significantly impact model fit, Scaled ML χ^2 Difference Test (2, $n = 152$) = 5.00, $p = 0.08$, although it showed a non-significant trend in this direction.

Table 7. Statistical Comparison of Nested Models

Model Tested	ML Scaled χ^2	df	Scaled ML χ^2 Difference Test	Δ df	p -value
M1	12.63	5	--	--	--
M2	8.86	3	3.87	2	0.14
M3	1.99	1	7.20	2	.03
M4	6.92	3	5.00	2	.08

Note. Models are contrasted with the model directly above it. Satorra-Bentler scaled chi-square difference testing conducted according to Bryant & Satorra (2012).

Path coefficients were also examined in each model using Benjamini-Hochberg's (1995) false discovery rate controlling step-up Bonferroni procedure to control Type I error rate. In M1, in which vascular risk predicted episodic memory, the path coefficient for this relationship was not significant, $\gamma = -0.10$, $p = 0.22$, indicating that vascular risk and episodic memory were not consistently associated in the sample. In M2, in which FC

was allowed to mediate the relationship between vascular risk and episodic memory, vascular risk remained unrelated to episodic memory, $\gamma = -0.10, p = 0.19$. Vascular risk was also unrelated to FC, $\gamma = -0.04, p = 0.61$. Finally, FC was not significantly related to episodic memory, $\beta = -0.17, p = 0.06$, although it showed a marginal trend in this direction, such that *higher* levels of functional connectivity between the PCC and VMPFC were marginally associated with *poorer* episodic memory performances. In M3, depressive symptoms were added to M2 as a second potential mediator. In this model, vascular risk remained unrelated to episodic memory, $\gamma = -0.08, p = 0.30$. In contrast, FC was significantly related to episodic memory in M3, $\beta = -0.18, p = 0.04$; stronger functional connectivity between the VMPFC and PCC was related to *poorer* performance on tests of episodic memory. Vascular risk was significantly related to depressive symptoms in M3, $\gamma = 0.17, p = 0.02$, such that higher levels of vascular risk were associated with more depressive symptoms. However, depressive symptoms were not related to episodic memory, $\beta = -0.13, p = 0.14$. In the final model M4, paths to and from FC were removed from M3, leaving depressive symptoms as the only mediator. Both vascular risk and depressive symptoms remained unrelated to episodic memory in this model, $\gamma = -0.08, p = 0.32$ and $\beta = -0.10, p = 0.28$, respectively.

FC and depressive symptoms were evaluated as potential mediators of the relationship between vascular risk and episodic memory according to recommendations by Baron & Kenny (1986) and through the use of bootstrapping of the indirect effect. In order for a variable to be considered as a mediator of a relationship between a predictor and outcome variable according to Baron and Kenny, four conditions must be met: 1) the

predictor variable must be related to the outcome, 2) the predictor variable must be related to the mediator, 3) the mediator must be significantly related to the outcome when also controlling for the effect of the predictor variable on the outcome, and 4) the indirect effect of the predictor variable on the outcome through the mediator must be statistically significant. Condition 1 was not met for either FC or depressive symptoms as potential mediators, because according to M1, vascular risk (the predictor) was not significantly related to episodic memory (the outcome). Condition 2 was met for depressive symptoms, because vascular risk (predictor) was significantly related to depressive symptoms (potential mediator) in M3 and M4. However, Condition 2 was not met for FC, because vascular risk was unrelated to FC (potential mediator) in each model tested. Condition 3 was inconsistently met for FC, because it was only marginally related to episodic memory in M2 when used as the sole mediator, but was significantly related to episodic memory in M3 when included with depressive symptoms. Condition 3 was not met for depressive symptoms, because they were unrelated to episodic memory in both M3 and M4.

It should be noted that recent writings on mediation recommend against using the first criterion proposed by Baron and Kenny (the predictor variable must be related to the outcome), because under certain conditions, there can be a significant indirect effect of a predictor on an outcome through a mediator, without the presence of a significant direct effect between the predictor and the outcome (e.g., Hayes, 2009). Therefore, a direct test of the significance of the indirect effect is recommended. This was conducted with bootstrapping using 5,000 resamples. The results supported the above conclusions; the

indirect effect of vascular risk on episodic memory through FC was not significant, 95% Bias Corrected and Accelerated (BCa) CI [-.0109, .0308], nor was the indirect effect of vascular risk on episodic memory through depressive symptoms, 95% BCa CI [-.0446, .0011]. The overall indirect effect of vascular risk on episodic memory through both mediators combined was also not significant, 95% BCa CI [-.0373, .0138]. Therefore, mediation was not supported for either functional connectivity or depressive symptoms.

Model goodness-of-fit, significance of incremental variance explained across different models, and model parsimony were considered in determining the most preferred model of those tested. Model 3 showed the strongest goodness-of-fit statistics considering both absolute and relative fit indices, although it was the least parsimonious model. The fact that the addition of depressive symptoms to M2 to create M3 significantly improved model fit suggests that M3 is preferred over M2. While the removal of FC from M3 to create M4 only marginally ($p = .08$) reduced overall model fit, there was a substantial change in specific measures of model fit from M3 to M4. Indeed, only two of M4's fit indices were in the acceptable range, compared to all of M3's indices being in the acceptable or nearly acceptable range. Therefore, although M4 is more parsimonious, its poorer fit suggests that M3 should be the preferred model. Although M3 is the model best supported by the data, it explained relatively small proportions of variance in study variables. M3 accounted for 0.17% of the variance in VMPFC FC, 2.9% of the variance in depressive symptoms, and 5.8% of the variance in episodic memory, and each of these variables had a significant amount of variance left

unexplained by the model (critical ratios for all psi estimates > 4.74 , p 's $< .001$). The final preferred model M3 is shown in Figure 12.

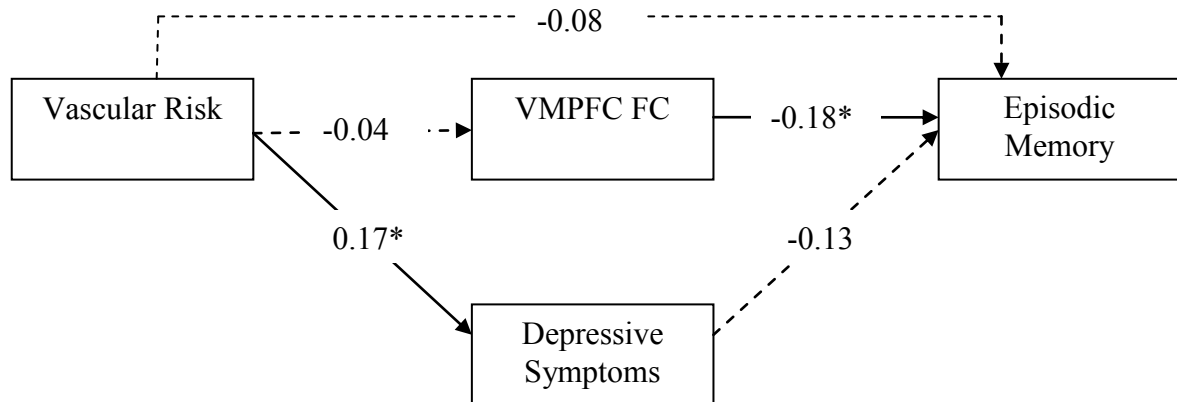


Figure 12. Final preferred model showing standardized path coefficients. Dotted lines are hypothesized but non-significant paths. $*p < .04$

CHAPTER 5

DISCUSSION

The present study examined posterior cingulate cortex (PCC) functional connectivity (FC) among cognitively intact older adults. The PCC is thought to be a major hub for the so-called default mode network (DMN), with other hubs including the ventromedial prefrontal cortex (VMPFC) and inferior parietal lobule (Andrews-Hanna et al., 2010; Buckner et al., 2008; 2009; Desphande et al., 2010; Greicius et al., 2003; 2009; Hagmann et al., 2008; Laird et al., 2009; Margulies et al., 2007; 2009; Moussa et al., 2011; Stawarczyk et al., 2011; Uddin et al., 2009). This network is more active during non-goal directed thought and reduces its activity during most task-oriented processing (Buckner et al., 2008; Gusnard & Raichle, 2001; Gusnard et al., 2001; Mazoyer et al., 2001; 2002; Raichle et al., 2001; Shulman et al., 1997). The DMN is thought to underlie such vital abilities as self-referential thought, autobiographical memory, and social emotional processing (Andreasen et al., 1995; Andrews-Hanna et al., 2009; Buckner & Carroll, 2007; Buckner et al., 2008; Buckner & Carroll, 2007; D'Argembeau et al., 2005; Gilbert et al., 2006; Grigg & Grady, 2010; Gusnard et al., 2001; Macrae et al., 2004; Mitchell et al., 2002; 2006; Oschner et al., 2004; Schacter & Addis, 2009; Schacter et al., 2007; Schilbach et al., 2008; Spreng et al., 2009; Stawarczyk et al., 2011; Svoboda et al., 2006).

Research utilizing functional connectivity (FC) analyses, which examine the degree of functional interrelatedness among distributed brain regions thought to compose a coherent neural network, have found altered DMN FC in different forms of dementia and mild cognitive impairment (e.g., Buckner et al., 2008; Celone et al., 2006; Greicius et al., 2004; Han, Arfanakis, Fleischman, Leurgans, Tuminello, Edmonds, & Bennett, 2011; Herholz, Salmon, Perani, Baron, Holthoff, Frolich, et al., 2002; Rombouts et al., 2005; Sorg, Riedl, Muhlau, Calhoun, Eichele, Laer, et al., 2007; Wang et al., 2006; 2007; Wu et al., 2007). In fact, reduced DMN FC, particularly in the posterior DMN subsystem that includes the PCC as its hub along with the hippocampus, is associated with declines in episodic memory (Andrews-Hanna et al., 2007; Han et al., 2011; He et al., 2013; Wang et al., 2010). Disruptions in DMN FC observed in dementias such as Alzheimer's disease (AD) have also been found to closely correspond with the localization of beta amyloid plaque development in the brain, neuropathological changes characteristic of AD (e.g., Buckner et al., 2005; 2009; Hafkemeijer, van der Grond, & Rombouts, 2012; Klunk, Engler, Nordberg, Wang, Blomqvist, Holt, et al., 2004; Mormino et al., 2011; but see Mormino, Brandel, Madison, Marks, Baker, & Jagust, 2012). This may suggest a causal role for beta amyloid development in disrupting DMN FC in AD (Buckner et al., 2005; 2009).

However, other recent research has suggested that the DMN may show abnormal FC among cognitively intact older adults in the absence of any known dementing process (Andrews-Hanna et al., 2007; Beason-Held, 2011; Buckner et al., 2009; Damoiseaux et al., 2008; Esposito et al., 2008; Gong et al., 2009; Grady et al., 2010; Hampson et al.,

2012; Hedden et al., 2009; Koch et al., 2009; 2010; Mevel et al., 2011; Mowinckel, Espeseth, & Westlye, 2012; Park et al., 2010; Sambataro et al., 2010; Wang et al., 2010; Wu, Wu, Yan, Chen, Zhang, He, & Yang, 2011; Wu et al., 2007; Ystad et al., 2010). The factors driving age-related disruption in DMN functional connectivity are unknown. One extremely prevalent health issue that may be important to consider is vascular risk, including hypertension, diabetes, and cigarette smoking. Vascular risk factors are known to damage both gray matter and the structural white matter fibers connecting gray matter regions throughout the brain, on which FC relies (Appel et al., 2009; Appelman et al., 2009; Bresser et al., 2010; Brickman et al., 2010; Bruehl et al., 2009; Burgmans et al., 2010; Correia et al., 2008; DeCarli et al., 1999; de Leeuw et al., 2002; Delano-Wood et al., 2008; Domino, 2008; Dufouil et al., 2001; 2005; Gons et al., 2010; Gottesman et al., 2010; He et al., 2010; Kennedy & Raz, 2009; Knopman et al., 2005; Kuller et al., 2010; Lazarus et al., 2005; Lee et al., 2010; Longstreth et al., 1996; 2000; Madden et al., 2009; Manolio et al., 1994; Murray et al., 2005; Raz et al., 2007; van Harten et al., 2006; 2007). Furthermore, vascular risks have also been associated with declines in episodic memory and other cognitive abilities (Bangen et al., 2009; 2010; Brady et al., 2005; Edelstein et al., 1998; Elias et al., 2005; Fillit et al., 2008; Fioravanti, 2012; Flicker et al., 2010; Harrington et al., 2000; Hill et al., 2003; Kalmijn et al., 2002; Kerola et al., 2011; Luchsinger et al., 2005; Paul et al., 2006; Reitz, Luchsinger, Tang, & Mayeux, 2005; Richards, Jarvis, Thompson, & Wadsworth, 2003; Sabia et al., 2008; Schinka, Belanger, Mortimer, & Graves, 2003; Singh-Manoux & Marmot, 2005; Starr et al., 2006; Stewart et al., 2006; Zade et al., 2010). While a small number of studies have investigated the

impact of vascular disease on FC in select populations (Duinkerken et al., 2009; Musen, Jacobson, Bolo, Simonson, Shenton, McCartney, et al., 2012; Sun et al., 2011; Zhou et al., 2010), the potential causal role for overall vascular risk in disrupting DMN FC in typical aging has not yet been explored.

Thus, the present study examined DMN functional connectivity among cognitively intact older adults using its hub, the PCC, as a seed region in FC analyses. A major goal was to examine the relationship of vascular risk, including hypertension, diabetes, and cigarette smoking, with FC of the DMN's PCC hub. A second goal was to examine the relationships of PCC FC with episodic memory among older adults. Third, the ability of PCC FC to mediate the relationship between vascular risk and episodic memory was examined using structural equation modeling. Finally, this mediational model was compared with one that included depressive symptoms as an alternative mediator of the relationship between vascular risk and episodic memory. Depressive symptoms were chosen because of their well-known relationship with cerebrovascular risk and disease (e.g., Flicker et al., 2010; Hakim, 2011; Lezak et al., 2004; Santos, Kovari, Hof, Gold, Bouras, & Giannakopoulos, 2009; Sneed & Culang-Reinlieb, 2011), and their impact on episodic memory performance (Bennett et al., 2004; Fioravanti et al., 2012; Hakim, 2011; Lezak et al., 2004; Sneed & Culang-Reinlieb, 2011).

It was predicted that using the PCC as a seed region in functional connectivity analyses would reveal significant functional associations with regions thought to belong to the DMN. This was supported overall, as the FC analysis identified several regions traditionally associated with the DMN, including anterior cingulate cortex/VMPFC,

medial and lateral parietal and temporal regions, and left hippocampus. The similarity of the current findings to those of other studies supports the reproducibility of the DMN across various samples in the literature, and suggests that FC analysis with a PCC seed region is a valid method for investigating the DMN. However, the PCC was also functionally connected to additional brain regions not typically associated with the DMN, including the basal ganglia, thalamus, and cerebellum. One possibility for this discrepancy is that the DMN may be more widespread than initially appreciated in earlier work. This is supported by recent research showing involvement of the cerebellum in the DMN (Grady et al., 2010; Habas et al., 2009; Krienen & Buckner, 2009; Sang, Qin, Liu, Han, Zhang, Jiang, & Yu, 2012; Wirth et al., 2011). In addition, several studies of healthy adults have found that regions traditionally associated with the DMN are activated in concert with the cerebellum during certain tasks, particularly episodic memory retrieval, a putative function of the DMN (e.g., Vandekerckhove, Markowitsch, Mertens, & Woermann, 2005). While the cerebellum's role in the DMN is receiving increasing support, the involvement of the basal ganglia and thalamus in the DMN requires further investigation.

An alternative explanation for the current findings of PCC connectivity with the cerebellum, basal ganglia, and thalamus, is that the DMN may become more distributed in old age, a notion that has garnered support in the literature (e.g., Beason-Held, 2009; 2011; Greicius et al., 2004; Meunier et al., 2009; Sun, Tong, & Yang, 2012). Several studies have found that the neural networks of older adults become less locally connected, instead showing more diffuse, distributed connectivity (e.g., Achard &

Bullmore, 2007; Matthaus, Schmidt, Benerjee, Schulze, Demirakca, & Diener, 2012; Micheloyannis, Vourkas, Tsirka, Karakonstantaki, Kanatsouli, & Starn, 2009; Sun et al., 2012). A related literature shows that older adults have more distributed and less specialized patterns of recruitment during task processing, termed dedifferentiation (e.g., Carp, Gmeindl, & Reuter-Lorenz, 2010; Dennis & Cabeza 2011; Duverne et al., 2008; Giovanello & Schacter, 2012; Goh, 2011; Matthaus et al., 2012; Morcom et al., 2007; Morcom & Fletcher, 2012; Park et al., 2004; Ramsoy, Liptrot, Skimminge, Lund, Sidaros, Christensen, et al., 2012; St-Laurent et al., 2011; Voss, Erickson, Chaddock, Prakash, Colcombe, Morris, et al., 2008). Dedifferentiation has been interpreted by some as a compensatory strategy to offset deleterious effects of aging and neurodegenerative processes, but by others as a sign or cause of age-related neural dysfunction and reduction in neural efficiency (e.g., Cabeza et al., 1997; 2002; Cabeza, 2002; Duverne et al., 2009; Goh, 2011; Grady et al., 1995; 2002; Gutchess et al., 2005; Li & Lindenberger, 1999; Logan et al., 2002; Morcom et al., 2007; 2012; Park et al., 2004; Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Lustig, 2005; Reuter-Lorenz & Park, 2010; Schiavetto et al., 2002), dependent upon whether the recruitment pattern is associated with better or worse functioning. However, whether these age-related changes specifically target the PCC's FC with the cerebellum, basal ganglia, and thalamus, as suggested in the current study, awaits further investigation.

Some studies have provided evidence supporting the basal ganglia's increased role in the DMN with age. For instance, Kelly and colleagues (2009) investigated the effects of L-dopa administration to young adults. One of the major sources of dopamine

in the brain involves nigrostriatal circuits originating from the substantia nigra in the midbrain, and projecting to the striatum of the basal ganglia (e.g., Kolb & Whishaw, 2009). Furthermore, dopaminergic transmission, particularly in striatal circuits within the basal ganglia, is known to be abnormal in aging, and is also associated with declines in cognition (e.g., Backman et al., 2006; Berger et al., 2004; Frank & Kong, 2008; Graybiel, 2008; Morcom et al., 2009; Mozley et al., 2001; Piefke & Fink, 2005). Kelly et al. (2009) found that administration of L-dopa was associated with reduced functional connectivity between the caudate and the DMN, and increased FC between the striatum and task-positive regions. This suggests that higher levels of dopamine promote the disruption of functional connectivity between the basal ganglia and the DMN in favor of strengthened connectivity between the basal ganglia and task positive networks. This concurs with the proposal that dopamine may increase the neural signal-to-noise ratio, allowing the basal ganglia to modulate DMN activity in favor of task-related networks to improve task performance (Kelly et al., 2009). These findings paralleled those of Nagano-Saito et al. (2008), who found that reductions in dopamine impaired the deactivation of the DMN during task performance, leading to an overactive DMN with low dopamine levels. Taken together, these findings suggest that age-related reductions in dopamine may disrupt connectivity of the DMN by increasing its functional connections with the striatum, impairing the brain's ability to switch from processing in the DMN to the task-positive networks. This would explain the current findings of striatal involvement in the DMN among older adults, as well as previous findings of impaired DMN deactivation and associated poor task performance among older adults (e.g., Andrews-Hanna et al., 2007;

Damoiseaux et al., 2008; Duverne et al., 2009; Esposito et al., 2008; Grady et al., 2006; Grady et al., 2010; Koch et al., 2010; Lustig et al., 2003; Miller et al., 2008; Park et al., 2010; Persson et al., 2007; Sambataro et al., 2010).

Hypothesis 2 predicted that PCC FC would be significantly related to episodic memory performance, particularly in medial temporal lobe (MTL) structures. This was generally supported, as several regions showed relations between PCC FC and episodic memory. Within the MTL, stronger functional connectivity between the PCC and a cluster including a small portion of the right parahippocampal gyrus was associated with better episodic memory performance. This concurs with other studies demonstrating the importance of intact connectivity between MTL structures and the PCC for episodic memory (Andrews-Hanna et al., 2007; Han et al., 2011; He et al., 2013; Wang et al., 2010). The parahippocampal gyrus and hippocampus are known to be important for associative learning and source memory (Lepage et al., 2000; Mesulam, 2000; Mitchell et al., 2009; Park et al., 2012; Qin et al., 2007). Source memory has been found to decline in typical aging and AD (see Mitchell et al., 2009, for a review). Thus, older adults with stronger connectivity between regions involved in source memory (e.g., parahippocampal gyrus) and posterior regions within the episodic memory DMN subsystem (e.g., PCC) may show stronger episodic memory performances, perhaps due to better associative encoding or utilization of associative cues for memory retrieval. In fact, some research has suggested that the aging brain may increase activity in the parahippocampal gyrus to compensate for activity declines in the hippocampus (e.g., Cabeza et al., 2004; Daselaar et al., 2006; Persson et al., 2012). The present results support the notion of

parahippocampal compensation to support episodic memory performance among older adults. However, this parahippocampal compensation cannot be attributed to declines in hippocampal connectivity in the current study, because no associations between PCC-hippocampal FC and episodic memory were found. It is important to note that PCC connectivity with most of the medial temporal lobes was surprisingly unrelated to episodic memory performance. Instead, the majority of regions where PCC FC was associated with episodic memory performance were in ventral visual cortex and subcortical regions.

Stronger functional connectivity between the PCC and the bilateral declive of the cerebellar vermis was associated with better episodic memory performance. This supports the increasing recognition of the cerebellum's important role in cognition (Stoodley & Schmahmann, 2010) and episodic memory (e.g., Andreason et al., 1999; Cabeza & Nyberg, 2000; Fliessbach et al., 2007; Hokkanen et al., 2006; Sang et al., 2012; Svoboda et al., 2006; Vandekerckhove et al., 2005). A meta-analysis by Svoboda et al. (2006) found that the cerebellum was involved in both a neural network associated with autobiographical memory retrieval, as well as one for semantic tasks. The authors suggested that the cerebellum may contribute to a broad range of cognitive abilities through its involvement in executive functioning. Indeed, the cerebellum has consistently been linked to working memory, and the right cerebellum may be particularly important for internal speech necessary for verbal working memory (Ackermann et al., 2007; Hokkanen et al., 2006; Marvel & Desmond, 2010; Stoodley & Schmahmann, 2010). In light of the above, one interpretation of the current findings is that increased functional

connectivity between the cerebellum and DMN may support stronger encoding of episodic memories through enhanced working memory processes, leading to better subsequent memory for the information. Alternatively, while regions of the cerebellum have been implicated in cognition, the posterior vermis, including the declive, may be particularly important for emotional processing (Stoodley & Schmahmann, 2010). Thus, a second interpretation of the current findings is that increased connectivity between the posterior cerebellar vermis and the DMN may bolster episodic memory in aging through increasing the emotional salience of information to be remembered.

In fact, other findings also suggested an important role for emotion in strengthening episodic memory among older adults. Specifically, better episodic memory was associated with stronger connectivity between the PCC and the left amygdala. The amygdala is a limbic region well known for its role in emotional processing, and is activated during the retrieval of emotionally-valenced memories (e.g., Dolan et al., 2000; Erk et al., 2003; Lezak et al., 2004; Mesulam, 2000; Mitchell et al., 2009; Svoboda et al., 2006). The amygdala has specifically been linked to modulating the emotional salience of memories during both encoding and retrieval (e.g., Lezak et al., 2004; Mitchell et al., 2009; St. Jacques et al., 2009). Research has suggested that the emotional salience of a memory, mediated by activity in the amygdala, increases the strength of the memory and its resistance to decay. Indeed, the amount of amygdala activity during memory encoding has been found to correlate with the amount of information later remembered (Mitchell et al., 2009). There is evidence that the benefit of emotion for memory may be reduced in old age, as recent work has suggested that the connectivity between the amygdala and

hippocampus declines among older adults (Matthuas et al., 2012). Following from this, the present results suggest that older adults may compensate for the disconnection of the amygdala from the hippocampus by increasing the connectivity between the amygdala and the PCC. A compensatory interpretation is further supported by the positive relationship between increasing amygdala-PCC connectivity and better episodic memory performances.

Overall, findings of increased connectivity between the PCC and structures important for emotional processing (e.g., cerebellar vermis, amygdala), and associations of these connectivity patterns with better episodic memory performance, suggest that strengthening the emotional salience of memories is important for optimal episodic memory performance among older adults. Research has found that emotional valence enhances subsequent memory (Fioravanti, 2012; Jacques et al., 2009; Mitchell et al., 2009), which has been attributed to enhancement of attention and perception in response to emotional stimuli (Mitchell et al., 2009). However, emotional enhancement of memory may only occur among older adults for positive emotions. Older adults have been found to pay less attention to negative emotional stimuli and show poor subsequent recall for negatively-valenced information, in contrast to improved recall of positively-valenced stimuli (Fioravanti, 2012). In addition, older adults have relatively preserved source memory for emotional information and are also more likely to use emotional information when making source memory attributions (Mitchell et al., 2009). It is possible that these effects are mediated by increased connectivity of the amygdala and cerebellar vermis with the episodic memory subsystem of the DMN among older adults.

In contrast to results linking vermal cerebellar regions with stronger episodic memory performance, other regions of the cerebellum, specifically Crus I and Crus II, showed the opposite pattern, in which increasing connectivity between these structures and the PCC was associated with worse episodic memory performance. Whereas the vermal cerebellum has been primarily associated with emotional processing, Crus I and II are thought to be important for cognition (Krienen & Buckner, 2009; Sang et al., 2012; Stoodley et al., 2010), particularly executive functioning and working memory (Habas et al., 2009; Krienen & Buckner, 2009; Sang et al., 2012). Some studies have suggested that Crus I and II may be involved in the DMN (Krienen & Buckner, 2009; Sang et al., 2012), although they have been most consistently implicated in the cognitive control network subserving executive functioning and working memory (Sang et al., 2012; Habas et al., 2009). In line with this notion, Fliessbach et al. (2007) found that greater activation in Crus I and II during encoding in an incidental learning task was associated with successful subsequent recall of studied words, which the authors attributed to the cerebellum's well-known role in verbal working memory processes.

However, the present findings suggest that increased connectivity between Crus I and II and the PCC is associated with *poorer* episodic memory performance among older adults. This finding may reflect dedifferentiation of the DMN to include regions typically involved in other functional networks. Age-related dedifferentiation has been linked to cognitive decline, presumably because reductions in the specialization of specific brain regions prevent the efficient processing of information that relies upon highly specialized neural networks in the younger brain (e.g., Achard & Bullmore, 2007; Goh et al., 2010;

Goh, 2011; Morcom et al., 2007; 2012; Park et al., 2004). Specifically, the current results may indicate that co-activation of the PCC with structures implicated in the cognitive control network (i.e., Crus I and II) may prevent efficient retrieval of episodic memories, which is normally mediated by the DMN (Daselaar et al., 2009; Henson et al., 2005; Huijbers et al., 2011; Kao et al., 2005; Kim et al., 2009; Miller et al., 2008; Otten & Rugg, 2001; Prince et al., 2005; Shrager et al., 2008; Vannini et al., 2011; Wagner et al., 2005; Weis et al., 2004). An alternative interpretation is that activation of the DMN during information encoding, when the DMN is typically deactivated in favor of task positive networks such as the cognitive control network, may impair the encoding of information into memory, leading to poorer episodic memory performances. In sum, the present cerebellar findings suggest that both compensation (in the cerebellar decline) and dedifferentiation (in Crus I and II) can not only occur simultaneously, but can also coexist within different subregions of the same brain structure, and have divergent implications for episodic memory performance.

The current results also implicate the putamen of the basal ganglia in episodic memory processes among older adults, as stronger connectivity between the putamen and the PCC was associated with better episodic memory performances. Although typically associated with motor functioning and implicit learning, the basal ganglia are becoming more investigated for their importance in higher order cognitive processing (e.g., De Jong et al., 2008; Svoboda et al., 2006; Qin et al., 2007; Yang et al., 2013; Ystad et al., 2010; 2011). The caudate and putamen have together been implicated in autobiographical memory (Svoboda et al., 2006) as well as in episodic memory function by several studies

with Parkinson's and Huntington's disease patients (see Ystad et al., 2010, for a discussion). The involvement of the basal ganglia in episodic memory may be secondary to the caudate's known role in executive functioning through its connections with the frontal lobes (e.g., Grahm et al., 2009; O'Brien et al., 2009; Qin et al., 2007).

However, some have specifically linked the putamen to episodic memory processes (Benisty et al., 2009; Camicioli et al., 2009), and have suggested that the involvement of the striatum in episodic memory cannot fully be explained through executive processes (Ystad et al., 2010). Further, neuroimaging studies have revealed that the basal ganglia and MTL comprise two parallel memory systems that can work together under certain circumstances, whereas in other circumstances they are competitive (Doeller et al., 2008; Foerde et al., 2006; Packard & Knowlton, 2002; Poldrack et al., 2001). Thus, the basal ganglia, and specifically the striatum, appear to play an important role in episodic memory beyond their involvement in executive functions. The current results suggest that older adults may preserve or improve episodic memory through increased connectivity between the putamen and the DMN.

However, in contrast to the current findings, Ystad et al. (2010) examined non-demented older adults and found that increasing functional connectivity of the putamen was associated with *poorer* episodic memory performance. This discrepancy in findings may stem from differences in the study samples. Although both samples were cognitively intact, the present sample was fairly old (mean age = 81 years), whereas the sample of Ystad et al. (2010) was much younger (mean age = 64 years), and included middle-aged individuals. Therefore, whereas it is less likely that the current sample included

individuals with prodromal dementia because of their advanced age and episodic memory performance a half standard deviation above age-adjusted norms, it is possible that the much younger sample of Ystad et al. (2010) included individuals at the very beginning of the dementing process, before normative cognitive decline is evident. In light of this possibility, the current findings may suggest that for healthy older adults, increased connectivity between the putamen and DMN is associated with better memory, reflecting a compensatory effect. The negative findings of Ystad et al. (2010) may instead reflect a transition from compensation to cognitive decline (in which FC is still increased, but becomes associated with poorer cognition as compensatory efforts fail) in a sample which may have inadvertently included individuals with incipient dementia.

The current analysis also identified several ventral visual regions in which FC with the PCC was significantly associated with episodic memory. Regions in which increased connectivity with the PCC was associated with better episodic memory included the bilateral fusiform and right middle occipital gyrus. Many studies have reported age-related changes in the structure and function of visual areas with advancing age (e.g., Goh, 2011; Hampson et al., 2012; Matthaus et al., 2012; Mowinckel et al., 2012; Tomasi & Volkow, 2012). For instance, Matthaus et al. (2012) found that during an episodic memory task, younger adults showed a high degree of hubness (i.e., a high number of functional connections with other regions) in occipital regions and the fusiform gyrus, but that the hubness of these visual regions was greatly reduced during the episodic memory task among older adults. Moreover, the associations between visual networks and the DMN may change with age. Onoda et al. (2012) found that advancing

age was associated with reduced connectivity between the DMN and visual networks.

The current findings suggest that older adults who show functional connectivity patterns similar to younger adults, with strong functional connectivity of occipital and fusiform regions, show better memory performance.

Other potential explanations for the above findings are suggested by consideration of the functional relevance of the ventral visual regions for memory processes. The ventral visual regions, including inferior occipital cortices and fusiform, extending into the inferior and middle temporal lobe, mediate the identification of visual stimuli (Mesulam, 2000). Similarly, the inferior and middle temporal gyri and fusiform have also been implicated in semantic processing and associative encoding (e.g., Lepage et al., 2000; Mesulam, 2000; Wirth et al., 2011). Therefore, the current findings may reflect the benefit of semantic associative encoding for episodic memory formation and retrieval. An alternative possibility is that older adults with stronger functional connections between the DMN and occipital cortices may be better able to utilize imagery and other visual-based mnemonics as encoding and retrieval strategies, which would in turn be associated with stronger episodic memory performance (Cabeza et al., 2000; Chun & Johnson, 2011).

Despite evidence for a positive relationship between connectivity with visual regions and better memory performance in older adults, relationships suggesting the opposite were observed in this study as well. Specifically, a cluster centering in the right fusiform and inferior temporal gyrus, and a second cluster in more dorsally located regions centering in left superior occipital lobe and precuneus, showed *negative*

associations between PCC FC and episodic memory. Increased connectivity between these regions and the DMN was associated with poorer memory performance. The right fusiform has been linked to a bottom-up attentional network involving ventral parietal regions (Burianova et al., 2012; Corbetta et al., 2000; Kincade et al., 2005). These attentional networks may be involved both in detection of salient stimuli in the environment, as well as bottom-up (i.e., uncued) retrieval of episodic memories (Burianova et al., 2012). Similarly, parieto-occipital regions have been implicated in reflective attention (Chun & Johnson, 2011). Reflective attention directs attention to internally stored representations, such as thoughts or memories, allowing them to be recalled and manipulated in working memory, among other related functions. Some have proposed that reflective attention may be organized in a way similar to the distinction between dorsal and ventral systems for top-down and bottom-up attention (Chun & Johnson, 2011). According to this notion, superior parietal regions support the controlled search for information in memory (i.e., top-down), whereas inferior parietal regions mediate the spontaneous recall of salient, detailed memories, similar to the capture of attention through bottom-up processes. The current findings may reflect a loosening of functional associations of the PCC to include regions involved in bottom-up and/or reflective attentional processes, including the fusiform, superior occipital lobe, and precuneus. The increase in FC between these regions and the PCC may impair episodic memory due to the interference of bottom-up attention with memory retrieval mediated by the DMN. This may occur due to external distractions capturing bottom-up attention

during memory retrieval, or due to the uncued retrieval of episodic memories that are irrelevant to the memory task at hand.

Hypothesis 3 predicted that vascular risk would show significant correlations with PCC functional connectivity. This was supported, as the connectivity between the PCC and several regions were significantly associated with number of vascular risk factors. One cluster, centering in the right caudate and thalamus, showed positive correlations between functional connectivity with the PCC and vascular risk. In other words, individuals with higher levels of vascular risk showed stronger connectivity between the PCC and these regions. This finding may reflect a compensatory response. Vascular risk is well-known to reduce subcortical metabolism and volume, including in the basal ganglia and thalamus (Almeida et al., 2008; 2011; Dai et al., 2008; Pascual et al., 2010; Strassburger et al., 1997) and to damage fronto-subcortical white matter connections (e.g., Grinberg & Thal, 2010; Kalaria et al., 2010; Maillard et al., 2012; Salat et al., 2012). The current findings suggest that the brain may compensate for vascular-related damage and disconnection of subcortical structures by increasing functional connectivity between subcortical structures and posterior cortical areas, such as the PCC. Baker and colleagues (2011) also found evidence of compensation involving the basal ganglia in response to vascular risk. In their study, cognitively intact older adults with pre-diabetes and Type 2 diabetes overrecruited the right putamen compared to non-diabetic older adults during memory encoding. The current study extends these results by suggesting that the brain can compensate for vascular risk through increasing functional connectivity, and that compensatory processes involve the caudate as well as the

putamen. This notion should be further investigated by examining associations between this altered pattern of connectivity and cognitive functioning. If it is indeed a compensatory process, then positive effects on functioning should be noted compared to adults who do not show this pattern of functional connectivity.

Two clusters showed negative correlations between connectivity and vascular risk, indicating that individuals with higher levels of vascular risk showed decreased functional connectivity between these regions and the PCC. The first cluster included the left Crus I and II and tuber of the cerebellum. Several studies have found changes in cerebellar structure with various vascular risks. For instance, Glodzik et al. (2012) found cognitively intact older adults with hypertension showed the strongest volume reductions in the cerebellum compared to individuals without hypertension, even after controlling for white matter hyperintensities. Similarly, Strassburger et al. (1997) found that middle aged and older adults with hypertension had more cerebrospinal fluid, suggestive of tissue loss, in the cerebellum than normotensive adults. Both cerebellar white and gray matter were also found to be reduced in older adults with diabetes and high serum glucose, with the most robust findings for cerebellar white matter reductions (Hoogendam et al., 2012). Finally, Brody and colleagues (2004) studied younger and middle aged smokers, finding lower gray matter density in the right cerebellum compared to nonsmokers. Our results coincide with those of these studies, and suggest that not only does vascular risk impact cerebellar structure, but it also negatively impacts the functional connectivity between the cerebellum and the posterior hub of the DMN. The fact that Crus I and II are strongly associated with executive functioning and working

memory also suggests that disconnection of these cerebellar regions from the DMN may mediate the cognitive declines associated with chronic vascular risk, a possibility that will require further investigation.

The second cluster showing negative correlations between PCC FC and vascular risk centered in the left inferior temporal gyrus, indicating that individuals with higher levels of vascular risk had reduced functional connectivity between the PCC and the left inferior temporal gyrus. In agreement with these findings, Chen et al. (2012) found middle aged and older adults with Type 2 diabetes to have gray and white matter volume reductions in superior, middle, and inferior temporal gyri, even after controlling for other vascular risk factors such as body mass index and hypertension. The current findings extend those of Chen et al. (2012) to include negative impacts of vascular risk on functional connectivity of the inferior temporal lobes with the PCC.

The lateralization of the findings related to vascular risk is noteworthy. The cluster showing a positive correlation between vascular risk and PCC FC was in the right hemisphere, whereas both clusters showing negative correlations were in the left hemisphere. This coincides with the hypothesis that the right hemisphere is preferentially involved in compensatory processes in response to reductions in neural integrity elsewhere in the brain (Han et al., 2007). However, some studies of vascular risk have found that the structure of the right hemisphere is disproportionately affected, whereas the left hemisphere is relatively spared (e.g., Brundel et al., 2010; Chen et al., 2012; Giannakopoulos et al., 2009). One way to reconcile these findings may be that the brain attempts to counteract vascular-induced declines in right hemisphere volumes by

increasing functional connectivity of the remaining neurons in the atrophied region.

Future research combining structural and functional imaging will be necessary to fully test this possibility.

The subsequent analyses involved structural equation modeling using Fisher z-transformed functional connectivity values extracted from the functional connectivity analyses. Hypothesis 4 predicted that the FC between the PCC and the ventromedial prefrontal cortex (VMPFC), inferior parietal lobule (IPL), and hippocampus would form a coherent latent variable representing the DMN. This was not supported, as the latent variable provided a poor fit to the data, and only some of the FC indicators loaded significantly on the latent variable. The FC values used in the confirmatory factor analysis represent the correlation in activity time courses between a single voxel in the PCC and a voxel in each of the VMPFC, IPL, and hippocampus. Although the coordinates for these voxels were taken from previous research on the DMN (Hedden et al., 2009), the brain region specified by the voxel coordinates may not be identical across studies due to subtle intersubject variability in brain structure and the use of smoothing during image preprocessing. The confirmatory factor analysis may have produced a stronger model with functional connectivity values from entire regions of interest instead of single voxels, which would also provide more reliable identification of DMN regions across studies. Because the latent DMN variable was not supported, subsequent analytic steps used the FC between the PCC and VMPFC as a proxy for DMN FC in measured variable path analyses.

Hypothesis 5 stated that vascular risk would negatively predict episodic memory in a path analysis, and that this model would fit the data better than the null model, predicting no covariation among the variables. This was not supported, as the model provided a poor fit to the data, and vascular risk was unrelated to episodic memory in each model tested. In contrast to other research (e.g., Bangen et al., 2010; Goldstein et al., 2008; Llewellyn et al., 2008), this study suggests that vascular risk may not have strong associations with episodic memory among cognitively intact older adults. One reason for the discrepancy between the current findings and others showing a relationship between vascular risk and episodic memory is the nature of the vascular risk variable used in the current analyses. As a composite variable representing the presence of three risk factors, this variable may not be as sensitive as other more comprehensive measures of vascular risk including other known risk factors, such as hyperlipidemia or body mass index. The use of a count variable with only 4 possible values (i.e., 0, 1, 2, or 3 vascular risk factors), may also have limited our ability to detect significant relationships due to range truncation and limited variability. In addition, this measure represented the presence of the risk factor at any point across the lifespan, and as such did not take into account whether the risk factors were current or historical. Some of the included risk factors (e.g., smoking) have been tied to cognitive decline only for current, but not historical risk (e.g., Almeida et al., 2011; Anstey et al., 2007; Peters et al., 2008; Reitz et al., 2005). The measure also did not account for the risks' severity or how well managed they were, which could have an effect on whether there is associated cognitive decline. Taking these issues into account may have produced a more sensitive measure of vascular load, which

may have shown stronger associations with episodic memory. In addition, although this study had an acceptable level of power according to rules of thumb in the field to be able to detect a small to moderate mediation effect, the relatively low levels of vascular risk present in the sample may have produced an effect size on episodic memory that was too small to detect at the level of power present in this study.

A second reason for the discrepancy between the current findings and those of previous studies examining vascular risk and episodic memory may be sample differences. The current sample was highly educated, or in other words, had high levels of cognitive reserve. Cognitive reserve, operationalized by factors such as education and occupation, is thought to allow the brain to continue functioning at its premorbid level despite the increasing presence of neuropathology in aging and disease (Stern, 2002, 2009; Stern et al., 2005). This implies that individuals with high cognitive reserve will show less impairment than an individual with lower cognitive reserve, despite the same level of neuropathology. This may explain why our sample, despite having a number of vascular risks, did not show an association between those risks and episodic memory. Another possible explanation is that our sample was nearly 100% Caucasian. Other racial groups, such as African Americans, are well known to experience higher levels of vascular risk, and studying these groups may reveal stronger associations between vascular risk and cognitive outcomes than studying these variables in other, less affected racial groups. It will be important for future studies to ensure a demographically diverse sample to address this issue.

A third possibility is that the present findings could have been a factor of our composite episodic memory variable, which collapsed across recall and recognition memory. It is well-known that recall and recognition involve divergent brain regions and are differentially impacted in dementias and other neurological diseases (e.g., Aggleton & Brown, 2006; Lezak et al., 2004; Mesulam, 2000; Metzler-Baddeley et al., 2011; 2012; Mitchell et al., 2009; Rudebeck et al., 2009). Vascular risk factors are more likely to impact recall memory, mediated by the frontal lobes, because of the impact of vascular risk on frontal-subcortical circuits (e.g., Lezak et al., 2004), whereas recognition memory is typically spared. Thus, the variability produced by combining different forms of memory could have prevented us from detecting a significant effect of vascular risk on memory, which we may have been able to detect had we examined recall and recognition memory separately. Alternatively, although vascular risk has been linked to declines in episodic memory, it is more consistently associated with decrements in processing speed and executive functioning (e.g., Lezak et al., 2004; Schmidt et al., 2005; van den Heuvel et al., 2006). It is possible that vascular risk may affect these domains first, and only impact episodic memory at higher levels of vascular burden. Because the levels of vascular risk in this sample were relatively low, this study may have found significant effects on cognition had it examined executive functioning or processing speed instead of episodic memory.

Hypothesis 6 stated that in a path model, vascular risk would negatively predict DMN functional connectivity and episodic memory. Because the latent DMN variable was not supported by the data, DMN connectivity was operationalized by the FC between

the posterior and anterior DMN hubs, the PCC and VMPFC, respectively. DMN connectivity was hypothesized to positively predict episodic memory in this model. Finally, this model was predicted to provide a better fit to the data than the model described in hypothesis 5. This hypothesis was partially supported. The addition of DMN functional connectivity as a mediator of the relationship between vascular risk and episodic memory improved model fit, but only to a marginal degree. Therefore, the relationships between vascular risk and DMN functional connectivity, and between DMN functional connectivity and episodic memory, only explain a small portion of variance in the data beyond that explained by the relationship between vascular risk and episodic memory. This could be related to the methodological issues described above, including the composite variables used for vascular risk and episodic memory, as well as the fact that the sample had relatively low levels of vascular risk, intact episodic memory, and high levels of cognitive reserve. Each of these issues could attenuate the strength of the relationship observed between study variables, making them more difficult to reliably detect.

Additional reasons for the relatively small contribution of relationships involving DMN functional connectivity to overall explained variance are revealed through examination of path coefficients. Vascular risk was unrelated to DMN functional connectivity in each model tested, partially explaining why the addition of DMN functional connectivity to the model accounted for a relatively small amount of variance in the data. Although studies investigating the relationship of specific vascular risks to functional connectivity have reported significant associations (e.g., Duinkerken et al.,

2009; Musen et al., 2012; Sun et al., 2011; Zhou et al., 2010), this is the first study to examine a composite measure of vascular risk in relation to the functional connectivity of the PCC among cognitively intact older adults. Vascular risk may have an earlier impact on connectivity of regions beyond the PCC, particularly between frontal and subcortical structures well-known to be affected by vascular risk (Grinberg et al., 2010; Kalaria et al., 2010; Maillard et al., 2012; Salat et al., 2012; Seidel et al., 2009). A recent study by Yi et al. (2012) found that patients with subcortical vascular mild cognitive impairment showed reduced amplitude of low frequency fluctuations in brain activity within the anterior portion of the DMN. The authors interpreted this finding to represent decreased spontaneous activity in these regions. In contrast, the posterior DMN subsystem showed increased amplitudes among MCI patients, which the authors interpreted as a compensatory response of the posterior DMN to vascular-induced pathological changes in anterior DMN networks (Yi et al., 2012). Following from these findings, the current study may have detected a relationship between vascular risk and DMN functional connectivity by examining functional connectivity within the anterior DMN network, instead of between anterior and posterior DMN hubs. An impact of vascular risk on connectivity of the posterior DMN and between posterior and anterior hubs may only occur at high levels of vascular burden.

Providing partial support to hypothesis 6, DMN functional connectivity was significantly related to episodic memory in some, but not all models. However, the direction of this relationship was the opposite of what was predicted. Specifically, stronger DMN functional connectivity predicted marginally *poorer* episodic memory

performances when used as the sole mediator. This relationship became fully significant in the model that also included depressive symptoms as an additional mediator. This may represent a classical statistical suppression effect (e.g., Gaylord-Harden, Cunningham, Holmbeck, & Grant, 2010; Tabachnick & Fidell, 2007). Classical suppression occurs when the relationship between an independent variable (IV) and the dependent variable (DV) becomes stronger with the addition of another IV (the suppressor variable). This is thought to occur because the suppressor variable, which is related to the other IV, but unrelated to the DV, partials out (or suppresses) the variance in the other IV that is unrelated to the DV (Gaylord-Harden et al., 2010; Tabachnick & Fidell, 2007). This thereby improves the predictive validity of the IV because of the removal of error variance unrelated to the DV. In support, the bivariate correlation of DMN functional connectivity (the IV) with the episodic memory residual variable (the DV) was $-.16$, but the magnitude of this relationship increased to $-.18$ when depressive symptoms (the suppressor variable) were included in the model. This suggests that depressive symptoms may be important to consider when examining the relationships between PCC functional connectivity and episodic memory because of their ability to account for error variance in the functional connectivity variable that is unrelated to memory (Gaylord-Harden et al., 2010).

The direction of the relationship between DMN functional connectivity and episodic memory is of note, because stronger functional connectivity was associated with *poorer* episodic memory. This is in contrast to several studies finding stronger DMN connectivity to predict better episodic memory performance among older adults (e.g.,

Andrews-Hanna et al., 2007; Han et al., 2011; He et al., 2013; Wang et al., 2010). The current findings may reflect a failed compensatory effort, in which those with worsening memory strengthen the connectivity between the posterior hub of the episodic memory DMN subnetwork and the anterior DMN hub as an attempt to sustain memory functioning. However, the conceptual understanding of compensatory effects implies that they should be associated with better cognitive performances, not worse (Morcom et al., 2012). Therefore, an alternative explanation may be that as the modularity of the DMN declines with age and distributed connectivity across its subnetworks increases (e.g., Sun et al., 2012), as indicated by stronger connectivity between its anterior and posterior hubs, episodic memory decreases. This potential reduction in specificity of DMN hubs coincides with the notion of age-related dedifferentiation of brain regions, which has been linked to impaired neural efficiency and associated cognitive declines among older adults (e.g., Achard & Bullmore, 2007; Duverne et al., 2009; Giovanello et al., 2012; Morcom et al., 2012; Sun et al., 2012). It is possible that the current study found evidence of dedifferentiation instead of compensation because of the advanced age of the current sample. It is possible that what initially begins as a compensatory response, associated with better cognition, may eventually progress to dedifferentiation and cognitive decline as age-related neuropathology continues to accumulate. Longitudinal research will be beneficial in examining whether compensation and dedifferentiation are temporally related in this way.

It was predicted that the addition of depressive symptomatology to the model described in Hypothesis 6 as an alternative mediator would not significantly improve

model fit, and that the removal of DMN functional connectivity from the model containing both mediators would significantly reduce model fit. The first part of this prediction was not supported, because the addition of depressive symptoms to the mediational model including DMN functional connectivity improved model fit. This indicates that depressive symptoms explain a significant amount of variance in the data above and beyond that explained by vascular risk and functional connectivity. However, when each path including depressive symptoms was separately added to the model, only the relationship between vascular risk and depressive symptoms contributed significantly to explained variance. The relationship of depressive symptoms with episodic memory was unnecessary and did not improve model fit. Moreover, the addition of depressive symptoms to the model did not eliminate the significant effect of DMN functional connectivity on episodic memory. In fact, as discussed above, the relationship between functional connectivity and episodic memory became stronger with depressive symptoms in the model. This suggests that while depressive symptoms are more closely related to vascular risk than is functional connectivity, functional connectivity is more closely related to episodic memory than are depressive symptoms.

The positive relationship between vascular risk and depressive symptoms observed in this study has been well demonstrated in the literature (e.g., Flicker et al., 2010; Hakim, 2011; Lezak et al., 2004; Santos et al., 2009; Sneed & Culang-Reinlieb, 2011). One hypothesis for this relationship that has been supported in the literature is that small vascular-induced lesions disrupt fronto-subcortical circuits important for emotion, leading to depression (Fioravanti, 2012; Santos et al., 2009). Moreover, depression may

act as an additional stressor, further exacerbating accumulation of vascular pathology, perhaps through an inflammatory process. An additional, but not necessarily opposing possibility is that a variety of genetic, health, medical, and psychiatric factors mutually influence vascular pathology and depression (Santos et al., 2009).

Several studies have also documented the negative impact of depressive symptoms on episodic memory performance (e.g., Bennett et al., 2004; Fioravanti et al., 2012; Hakim, 2011; Lezak et al., 2004; Sneed & Culang-Reinlieb, 2011). However, this effect was not found in the current study, which may have occurred for several reasons. First, the sample reported a low number of depressive symptoms overall, with an average of less than one endorsed symptom over the course of the longitudinal study from which the data for the current study were drawn. Thus, the present sample was by no means depressed. Given the assumption that more severe cases of depression would be more likely to experience resultant cognitive declines, it may be that the low level of depressive symptoms endorsed by the sample limited any effect that may have been observed with episodic memory. In addition, our sample was fairly highly educated, and had episodic memory performances about 0.5 standard deviations above age-based norms. The high level of cognitive reserve in our sample and inclusion of only cognitively intact individuals may have limited the size of the effect of depression on episodic memory performance. This effect may have been present had we investigated those with mild cognitive impairment or dementia, who already show declines in episodic memory which may be more likely to be exacerbated by depression.

The second part of hypothesis 8 was partially supported, because the removal of DMN functional connectivity from the model including depressive symptoms as a mediator showed a marginal trend to reduce model fit. Given that the path from vascular risk to DMN functional connectivity was never significant in any model tested, but the path from functional connectivity to episodic memory was significant (albeit inconsistently) in the models, it is likely that the removal of the functional connectivity-episodic memory link is what drove this effect. Overall, these findings suggest that while depressive symptoms are important to include in the model because of their relation with vascular risk, functional connectivity between the PCC and VMPFC is also of likely importance in explaining the data due to its relationship with episodic memory.

Finally, it was predicted that DMN connectivity would partially mediate the relationship between vascular risk and episodic memory. This was not supported, because the conditions to satisfy mediation proposed by Baron and Kenny (1986) were not met for DMN functional connectivity or for depressive symptoms, a conclusion which was further strengthened by bootstrapping of the indirect effect. Regarding the Baron and Kenny criteria, vascular risk was unrelated to episodic memory in this study, although recent writings argue against using this criterion to establish mediation (e.g., Hayes, 2009). In addition, vascular risk was not related to DMN functional connectivity, violating an additional criterion for mediation. Depressive symptoms also violated an additional criterion for mediation, because it was unrelated to episodic memory when vascular risk was included in the model. Furthermore, bootstrapping of the confidence interval for each of the indirect effects of vascular risk on episodic memory through

DMN FC and depressive symptoms revealed non-significant effects. Therefore, although DMN functional connectivity showed a significant relationship with episodic memory, it is not a mediator of the predicted relationship between vascular risk and episodic memory. Similarly, although depressive symptoms were significantly related to vascular risk, they did not mediate the predicted relationship between vascular risk and episodic memory.

There were some limitations to this study that are important to note. Although the sample was relatively large for a neuroimaging study and was estimated to provide sufficient power (i.e., .80) to detect a small to moderate mediation effect using the approach recommended by Fritz and MacKinnon (2007), it is possible that there were significant effects present that were too small to reliably detect. The possibility of small effects may be more likely in the current study given the diverse nature of the variables (i.e., historical, neuroimaging, and performance-based variables). In addition, the study sample was fairly homogenous. It will be particularly important to examine the current relationships in diverse samples which include groups at higher risk for vascular disease, such as African Americans. It will also be important to have a diverse sample in terms of education, as the current sample was highly educated, which may have impacted results due to cognitive reserve.

Although all participants were cognitively intact, it is possible that this sample included individuals in the beginning stages of dementia. If so, this may create additional variability in the data that would attenuate the effect size of hypothesized relationships, and would also prevent conclusions regarding typical aging from being drawn from the

results. However, the advanced age of this sample and episodic memory performance half a standard deviation above age-adjusted norms argues against this possibility, and suggests that the sample represented healthy aging. An additional limitation inherent in research that examines typical aging is that of eliminating individuals with cognitive impairment and dementia from the sample. It may be that the hypothesized relationships between vascular risk, DMN functional connectivity, and episodic memory would be stronger in individuals with dementia, and by focusing exclusively on cognitively intact adults, these relationships were not detected.

Moreover, it may be that individuals with cognitive impairment have higher levels of vascular risk than cognitively intact adults, explaining the relatively low levels of vascular risk present in the current sample. Such a restriction of range may reduce the possibility of detecting significant effects that exist in the data, particularly if these effects are stronger for individuals with high vascular load. Future work in this area should seek to include samples with a wider range of vascular health. Toward this end, it may be beneficial to oversample individuals with high levels of vascular risk instead of using an epidemiological, community based approach to sample recruitment.

As previously mentioned, the composite variable of vascular risk may not have been sensitive enough to detect the effects of vascular risk on memory and functional connectivity. One improvement would be to include information on the chronicity of the risk factor, whether it's current or historical, and whether it is well-managed through a treatment regimen. These issues are important to consider in determining the likelihood for the vascular risk factors to impact cognition. In addition, although hypertension,

diabetes, and cigarette smoking are vascular risk factors with well-documented ties to cognition, it will also be important to examine vascular risk factors beyond these, including hyperlipidemia and body mass index.

An additional limitation was that the composite episodic memory variable collapsed across divergent forms of memory (i.e., recall and recognition) that are known to rely on different circuits in the brain. As such, this may have introduced additional variability into the composite variable and prevented detection of significant effects that would have been apparent had each aspect of memory been examined separately. It will be important for future research to explore differential contributions of vascular risk to impairment in memory recall and recognition, as well as whether the relationships with PCC functional connectivity and depressive symptoms differ according to this distinction.

A final limitation involves the use of path models to assess mediation hypotheses. Path models assume that each construct is measured perfectly and without error, which is clearly unrealistic for such abstract constructs as vascular risk, depression, memory, and DMN functional connectivity. In contrast, methods such as latent variable path analysis use multiple measures of each construct, which allows the quantification of reliability across measures of a given construct instead of assuming perfect reliability. This allows the analysis to partial out the variability in each construct indicator that is not shared with other indicators of that construct (i.e., variability that is unrelated to the latent construct of interest). As a result, only the variance that is shared among indicators of a construct (i.e., the latent variable) is used in the analysis. If the variance unrelated to the construct

of interest is not partialled out, but is used to predict other variables as is done in path analysis, several negative effects can occur due to the introduction of error into the data. Importantly, this can reduce the overall fit of tested models as well as the size of path coefficients. Therefore, the significance of hypothesized relationships and fit of the tested mediation models in the current study may have been strengthened had multiple measures of each indicator been combined in a latent variable path analysis. Future research should utilize multiple diverse measures of vascular risk, depression, and memory to provide a more varied assessment of each construct that would then lend itself to the use of latent variables in analysis.

Beyond the suggestions for future research given to improve upon this study's limitations, future research should also consider the impact of vascular risk on cognitive abilities beyond episodic memory, as well as whether connectivity within the DMN explains this relationship. An important domain to consider would be executive functioning, which is known to be impacted by vascular risk. It will also be vital to investigate DMN nodes beyond the PCC, particularly because of the propensity for vascular risk to impact frontal-subcortical circuits. Along these lines, examining vascular-related alterations in the anterior subnetwork of the DMN may be a fruitful line of inquiry. In addition, an important avenue for future work will be to determine whether the structure of the DMN itself changes at higher levels of vascular risk, perhaps in a compensatory process or as part of dedifferentiation. Approaches utilizing multi-group structural equation modeling may be particularly powerful for directly testing this possibility. Finally, the current study suggested important roles for subcortical structures,

including the basal ganglia and cerebellum, in both the DMN and episodic memory. The roles of these structures, and whether their contribution changes with age, should be the focus of future work in this area.

Bearing in mind the limitations of this study, it nevertheless has important implications for this area of research. This study suggests that intact DMN connectivity is important for episodic memory functioning among cognitively intact older adults, and is affected by vascular risk, particularly in subcortical regions. Although vascular risk did not show a significant relationship with episodic memory in this study, its significant relations with DMN functional connectivity still underscore the detrimental impacts of vascular risk on the brain, and highlight the importance of early and consistent management of these modifiable risk factors for optimal neural functioning. The current findings also suggest that the aging brain can evidence simultaneous compensatory increases in functional connectivity associated with better memory, as well as increases in connectivity that are detrimental to cognition, suggesting dedifferentiation of specialized brain regions. Compensatory and dedifferentiation processes were even found to occur in different regions within the same brain structure. This implies that future neuroimaging work of healthy aging should account for this complexity by investigating associations of functional connectivity with cognitive performance. Longitudinal research will be vital in determining whether compensation and dedifferentiation represent opposite ends on a continuum of age-related changes in functional connectivity within the brain, and what factors predict conversion from beneficial compensation to detrimental dedifferentiation with age. Importantly, the absence of a relationship between vascular

risk and DMN functional connectivity in path analyses suggests that other factors beyond the vascular risks considered here may be driving age-related declines in DMN functional connectivity. Future work should consider other lifestyle variables, such as diet, exercise, and cognitive activity, in addition to the vascular risks suggested above, to pinpoint the forces driving declines in DMN functional connectivity with age. The identification of factors responsible for disruption of large-scale neural networks with age will be the first step in preventing their impact on neural functioning and cognition among older adults.

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